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FELLOWSHIP AND CITIZENSHIP*

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DISTINGUISHED guests, members of the College, ladies and gentlemen:

We are gathered this evening in annual convocation for the purpose of doing honor to those who have richly deserved honor at the hands of this College. They include those who have distinguished themselves as physicians, teachers and scientists, or in the cause of Internal Medicine and of this College; also a great American who has given and is giving outstanding service to his country and to mankind. Particularly are we honoring some 349 physicians, upon their completion of a long and rigorous training and the fulfillment of the exacting requirements of the College, by admitting them to our Fellowship. It is to you who are about to become our Fellows in The American College of Physicians that I wish to address myself.

Congratulations are certainly in order, in the first instance, upon the educational achievements which such Fellowship implies. Few disciplines involve so long and arduous a course of undergraduate training as does medicine. Then, after receiving the degree of Doctor of Medicine, you pursued at least six more years of graduate training, including a year of internship, three years of residency and two years of special practice under conditions of prescribed standards before you were admitted to Associate membership. Your professional qualifications had to be proved to an American Specialty Board by two thorough examinations that resulted in your certification as specialists. Then as Associates you served an apprenticeship of from not less than three to as many as 10 years before you and your professional attainments passed the scrutiny of the Committee on Credentials. What a far cry this is from the days of not yet half a century ago when Doctor X could take a trip to a European medical center and upon

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his return, after a few months or even weeks, could announce in his hometown newspaper that he was now specializing in such-and-such a field.

More than just educational criteria, you had to meet at every stage of your advancement inquiries as to your character, probity and professional ethics. Before you became an Associate, and again before you could become a Fellow, the name of each one of you was sent to every Master and Fellow of this College in the United States, Canada, Central America, Cuba and Mexico with a prepaid return envelope should he wish to object to you on any grounds. This doesn't mean that one Fellow could blackball you and deny you an entry into the College, but it does mean that every objection would call for a searching study and clear refutation before you were accepted. The letters F.A.C.P. which you will be privileged to set after your name therefore have a deep significance: they tell the world, lay as well as professional, about your qualifications as a person and as a physician—they are the hallmark of what is best in both. Use them with pride and strive ever to be worthy of them.

But Fellowship in this College is not just a matter of what you are and what you have achieved. Even more is it a matter of what you will be. Implicit in Fellowship are certain responsibilities and obligations which you assume tonight and which will be determining factors throughout your professional career.

There is, of course, the matter of your continued self-education. A prime objective and a major achievement of the medical profession—and for the enlightenment of our fellow citizens it ought also to be more often our boast—is its provision for, and insistence upon, the acquisition of new and greater scientific knowledge by its members. This includes the whole structure of specialist training and the certification upon examination by the 19 American Specialty Boards. In the field of general medicine, the American Academy of General Practice requires of its members that to hold their membership they must receive 300 hours of approved postgraduate instruction in each triennium for a total of 30 years. All medical instruction of physicians in this country after one year of internship is a self-imposed discipline, arranged, administered and paid for by the physicians themselves, not by our Government. Indeed, our Government seems not to have too much concern about who practices what brand of healing: witness the fact that a license to practice medicine, once obtained, permits its holder to engage in any form or procedure of medical activity for the rest of his life, regardless of whether he acquires a single new thought or skill, or discards a single outmoded idea. I hasten to say, we have no worries about you on that score, for your advancement to Fellowship was contingent upon your demonstrated capacity for continued professional growth.

Beginning even in your days of internship, you have increasingly taken part in the education of young physicians. Today most of you are engaged in the training of residents, and from your ranks are largely recruited those

to whom is entrusted the clinical teaching of medical students. It is a triple responsibility, for it involves not merely the imparting of knowledge, but also the quickening of a spirit of inquiry and research, and, above all, the inculcation of the highest ethical standards. In all of this you are not just the preceptor but also the exemplar: not only what you teach but also how you live is what matters.

This College, the furtherance of its aims and objectives, the upholding of its ideals—these, too, are your responsibilities. Take an active part in its regional meetings and in its Annual Sessions. Scan carefully the young physicians in your community and then bring those who are worthy into our membership. Remember that when you propose someone as an Associate in this College, by such sponsorship you assume an interest in and responsibility for his progress that should culminate in his achievement of Fellowship. From now on, you are the College, and one day soon we who face you tonight will be happy to welcome you to these posts of leadership.

Now let me discuss with you some aspects of the role of a Fellow as a citizen. I do so for two reasons: Today as never before in their history, our respective countries have need of our active, our sustained, our fullest support to preserve for us and for our children the way of life that has been our heritage. And we as physicians have been particularly favored with training in special skills, and even more with understanding of the needs of others. We have received much; of us will much be required.

There is no need to speak to you of service at the community level. The whole life of the physician is so engaged. As Fellows of this College we renew our pledge to place the welfare of our patients even above our own and to extend freely our professional aid to the unfortunate.

But I do wish to stress service at the national level. The world of today is sharply divided into two camps. Our group is dedicated to the principle that man has been endowed by his Creator with certain inalienable rights, including life, liberty and the pursuit of happiness, and that governments derive their just powers only from the consent of the governed. Our opponents not only deny that principle but also challenge our right to hold it, nay, our very right to existence. Throughout the world and on every front that struggle for our survival has been joined.

The term "cold war" has unfortunately conveyed to many a concept of solely military connotations—that all we need is enough bombs and rockets, planes, guns and ships to stay the hand of the aggressor. If only it were as simple as that! But the struggle has been joined on every front—economic, social, philosophic and religious—a struggle for the hearts and minds of men.

Our survival in that struggle is a matter of the collective security of the free world; our defense on this continent is inseparable from the defense of every individual, of every inch of ground, in the free world. When any part of the free world falls, our own ability to defend ourselves is lowered in proportion.

In that struggle the United States finds itself with the role of leadership imposed upon it by the hand of destiny. How we acquit ourselves in that role, how we and our sister nations of the free world will meet the challenge of this hour, will seal the future of mankind.

The greatest handicap that besets us of this continent today is a widespread lack of knowledge among our citizens of the manifold problems of our friends in the other parts of the world. It is an ignorance born of our provincialism that in turn grew out of our geographic isolation. But geographic isolation has been wiped out by modern means of travel and communication. Fifty years ago, on a walking tour in the Black Forest, if I asked how far it was to the goal of the evening the answer would be, "Six hours," the time it would take to walk there. Today distance is still measured in time, but in six hours we cross oceans and continents. The most distant foreigners of then are our neighbors of today. But our mental isolation still exists.

Coupled with it is all too generally a softening of our moral, our spiritual fiber, the result of the softness of our living and the relative lack of struggle to achieve the blessings we enjoy. True, there are millions of us who learned our lessons in the hard school of war and adversity, but attrition takes its inexorable toll, and each year new millions of untaught children successively dilute our numbers. We forget that freedom is not something that we can easily pass on to our children. Freedom is something that must be won anew by each generation.

Here lies a major challenge for us all. There is a certain need for military training in the present scheme of things, even though it is debatable how general such training should be. But there is no scintilla of doubt about the need for *universal* training in citizenship and in the requirements set by our international responsibilities.

I would like to suggest one phase of such universal training. Each one of you knows that, even if there were no State laws to require it, a medical school education must be supplemented by a hospital internship before the young physician engages in the practice of medicine. By the same token, the education of young Americans, or Canadians, or Cubans or Mexicans, or Panamanians, or any others, is not really complete until they have served for a time in an apprenticeship in a foreign land. The idea is not new: the training of young businessmen, for example, has made use of this device in many countries. But its implementing and programming at our own national level would be new. This could be done in the Department of State by a new Section for Junior Ambassadors. An important by-product of such a plan would be a growing pool of capable linguists which today we so sadly lack.

Now physicians as a group have a better record in national service than does any other group that I can think of, chiefly because of the Doctor Draft Law. There are many among you who know whereof I speak. But there

are also many and increasingly more young physicians who have not had this experience. More is the pity, because medicine speaks a universal language, and the physician is in consequence the best ambassador of goodwill. There are many outlets in foreign lands through which any number of our young physicians could find such experience. Let me cite only a single small but very important one: there ought to be an American physician in every American Embassy of the world. Yet today not half-a-dozen physicians are so stationed.

Now I know full well that those of you who have not served overseas are not in a position at this late date to take on such an assignment. (Of course, if there are any exceptions, let me assure you I could recommend to you some splendid places later this evening.) Nevertheless, each one of you can do your country a tremendous service in the years ahead. You could put this idea of foreign sojourn in the minds of all your medical students, your interns and your residents. Many of you are teaching young physicians who are coming to us from other lands in ever-increasing numbers. (Here again I note with pride the achievement of this College in promoting international good-will as well as in furthering the cause of medical education through its program of Latin-American Fellowships with the aid of the Kellogg Foundation.) Make these young foreign physicians your special charge and interest. Bring them into your homes that they may truly gain your friendship and you theirs. Try to learn from them about their homelands and their problems. Better still, on your holiday visit their countries and see those problems at first hand. If you do, you may even realize that the type of medicine you have been teaching them isn't really what they have needed most. Above all, you will be helping to lay the foundation of goodwill and understanding on which alone can be reared the edifice of a lasting peace.

This day, therefore, is not merely the close of a chapter of training and preparation in your lives. It is even more than the formal entry into the period of your greatest usefulness and service. Let it be the call, nay, the challenge of destiny, to you and to us all.

One week ago today was the anniversary of the death in 1915 of a young Englishman who at the age of 27 had already achieved greatness as a poet. Dying of blood poisoning while serving as a Lieutenant, Royal Navy, in a transport bound for the Dardanelles, he was buried on the little Greek island of Skyros, lending prophetic fulfillment to the lines he had written only a few months before:

> "If I should die, think only this of me:
> That there's some corner of a foreign field
> That is for ever England."

Let us accept the challenge of our time, as Rupert Brooke did his, when he sang:

> "Now God be thanked who matched us with His hour."

BIOCHEMICAL AND GENETIC ASPECTS OF PRIMAQUINE-SENSITIVE HEMOLYTIC ANEMIA *

By Alf S. Alving, *Chicago, Illinois,* Robert W. Kellermeyer, Alvin Tarlov, *Joliet, Illinois,* Stanley Schrier and Paul E. Carson, *Chicago, Illinois*

Acute hemolysis, which may destroy half the red cells within a few days, occurs in approximately 10% of otherwise healthy American Negroes, very rarely in Caucasians,[1, 2, 3] when 30 mg. primaquine base (twice the dose necessary to cure vivax malaria) are administered daily. Hemolysis is self-limited and is a function of cell age, the older cells being the more susceptible.[4, 5] Sensitivity to the drug has a familial distribution.[6] The erythrocytes of sensitive individuals are normal morphologically, and no abnormal erythrocyte antibodies have been detected.[7, 8] Sensitive individuals react similarly to ingestion of a growing number of agents, including sulfanilamide,[8] nitrofurantoin (Furadantin),[9] furazolidone (Furoxone),[10] naphthalene,[11] vitamin K [12] and fava beans.[13] Because the initial investigations were carried out with primaquine by Hockwald and collaborators in 1952, we have referred to this syndrome as "primaquine-sensitive hemolytic anemia." [1]

At least five biochemical abnormalities characterize the intrinsic erythrocytic defect (table 1). Primaquine-sensitive erythrocytes characteristically are deficient in reduced glutathione (GSH),† [14] which is unstable in vivo.[15] When primaquine is administered to sensitive individuals, an acute fall in the reduced glutathione content of their erythrocytes precedes the major hemolysis.[16] The reduced glutathione of primaquine-sensitive erythrocytes also is unstable in vitro, and falls sharply when the cells are incubated with acetylphenylhydrazine. This in vitro reaction forms the basis for the "glutathione stability test," which Beutler has devised for detection of primaquine-sensitive individuals.[17] In 1956 Carson and his co-workers showed that hemolyzates of primaquine-sensitive erythrocytes were deficient

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† GSH, reduced glutathione; TPN, triphosphopyridine nucleotide; TPNH, reduced triphosphopyridine nucleotide; DPNH, reduced diphosphopyridine nucleotide; DPN, diphosphopyridine nucleotide; GSSG, oxidized glutathione.

in glucose-6-phosphate dehydrogenase.[18] More recently, Schrier and his associates have found that sensitive cells have increased amounts of glutathione reductase and aldolase.[19, 20, 21]

The relationship of the known enzymic abnormalities to the two main pathways of carbohydrate metabolism within the red cells is illustrated in figure 1. Primaquine-sensitive erythrocytes are deficient in glucose-6-phosphate dehydrogenase, the enzyme catalyzing the initial oxidative reaction of the hexosemonophosphate shunt. These erythrocytes would therefore reduce less TPN to TPNH. TPNH is currently considered to be the coenzyme essential for reductive biosynthetic processes.[22] Erythrocytes deficient in TPNH might be unable adequately to reduce glutathione,[23] detoxify drug products,[24] or synthesize the fatty acids [25] concentrated in the erythrocyte membrane, and would therefore be susceptible to hemolysis. However, since primaquine-sensitive erythrocytes hemolyze only when they are exposed to drug, mechanisms may exist which partly compensate for inadequate TPN reduction.

TABLE 1

Biochemical Abnormalities in Primaquine-Sensitive Erythrocytes

1. Low reduced glutathione (GSH) but normal oxidized glutathione (GSSG)
2. Unstable GSH which falls
   In vivo when hemolytic drug is administered
   In vitro when RBC are incubated with acetylphenylhydrazine
3. Deficiency of glucose-6-phosphate dehydrogenase
4. Increase in glutathione reductase
5. Increase in aldolase

Aldolase supplies substrate for the oxidative phosphorylation of the Embden-Meyerhof glycolytic pathway, thereby providing energy and potential reducing power (figure 1). Increased aldolase might, by allowing more glucose utilization via the Embden-Meyerhof pathway, provide a relative increase of DPNH. In certain circumstances DPNH may substitute for TPNH, as has been shown by in vitro studies of glutathione reductase in human hemolyzates.[26, 27] Theoretically, by supplying increased DPNH, increased aldolase may partly compensate for a postulated deficiency of TPNH.

Glutathione reductase is an enzyme whose distribution in mammalian tissues roughly parallels that of the oxidative enzymes of the hexosemonophosphate shunt.[28, 29] It serves to reduce glutathione and to oxidize TPNH. Increased glutathione reductase may partly compensate for:

1. Deficient glucose-6-phosphate dehydrogenase, by providing greater availability of its obligatory co-enzyme, TPN, theoretically allowing the deficient enzyme to work at its maximal rate [30] (figure 1).

2. The deficiency in GSH, by regenerating GSH more effectively (using either TPNH or DPNH) after its oxidation is brought about in the erythrocyte (figure 1).

These biochemical abnormalities, alone or in combination, probably with others as yet undiscovered, may account for the phenomenon of hemolysis and provide a means for studying the mode of genetic transmission.

The glutathione stability test was originally standardized by Beutler on five known primaquine-sensitive individuals and seven individuals known to be nonsensitive to primaquine, all of whom were males.[17] It has been employed in several investigations for the purpose of studying the genetic basis for the transmission of sensitivity to primaquine hemolysis. Childs and his co-workers recently[6] reported the results of an extensive and careful investigation using the in vitro glutathione stability test, in which both randomly selected Negroes and families of sensitive individuals were tested.

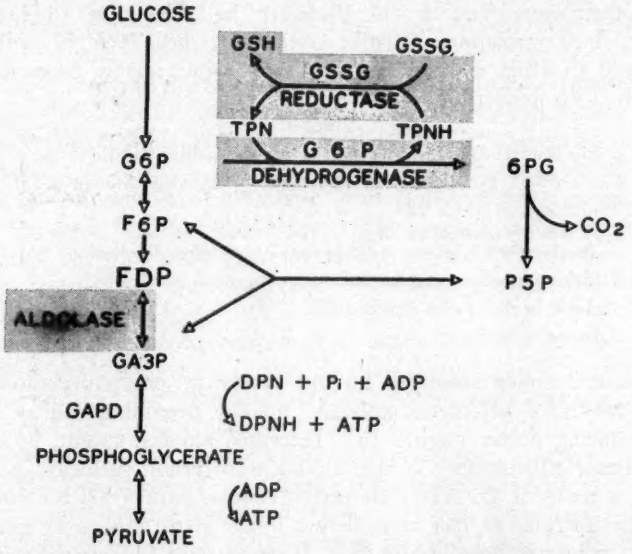

FIG. 1. Schematic and abbreviated pathways of carbohydrate metabolism in human erythrocytes. Cross-hatching indicates known abnormalities in primaquine-sensitive erythrocytes.

In the random survey they found that the incidence of "reactors" was 15% in males and 2% in females. This distribution of "reactors" and "normals" was bimodal. About 5% of females and 2% of males, however, showed only partial instability of the reduced glutathione in their erythrocytes, and were classified as "intermediates." The "intermediate" group was considered to be heterozygous. These investigators concluded that the inheritance of primaquine sensitivity in Negroes was most likely through a sex-linked gene with incomplete dominance, but they could not exclude a sex-limited autosomal gene showing dominance. Recently Gross et al.,[31, 32] employing both the glutathione stability test and an assay for glucose-6-

TABLE 2

Primaquine-Induced Hemolysis in a Random Population of Negro Children and Young Adults

Females	
Total tested	69
Percentage positive	8.7%
Males	
Total tested	72
Percentage positive	11.1%

phosphate dehydrogenase, presented further observations which were compatible with the conclusions of Childs and his co-workers.[6]

Relatively few subjects studied by either group had experienced clinical hemolysis. It was assumed that the in vitro instability of reduced glutathione accurately reflected in vivo sensitivity to primaquine, fava beans,

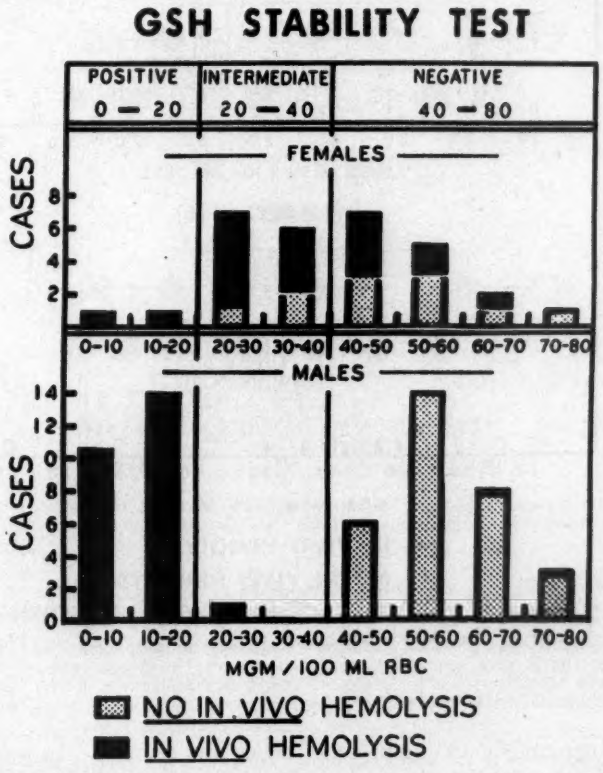

FIG. 2. Relationship of in vivo primaquine hemolysis to the glutathione stability test. Selection was made on the basis of known response to primaquine in 87 cases. The interpretation of GSH stability test results ("positive," "intermediate," "negative") corresponds to divisions arbitrarily established by Childs et al.[6] and Beutler.[17]

naphthalene and other drugs. It was implied that "intermediates" were partially sensitive.

In coöperation with Hodgkinson * and Payne,* we have recently studied the incidence of hemolysis after primaquine administration in 141 randomly selected Negroes ranging from two to 20 years of age. In this group there

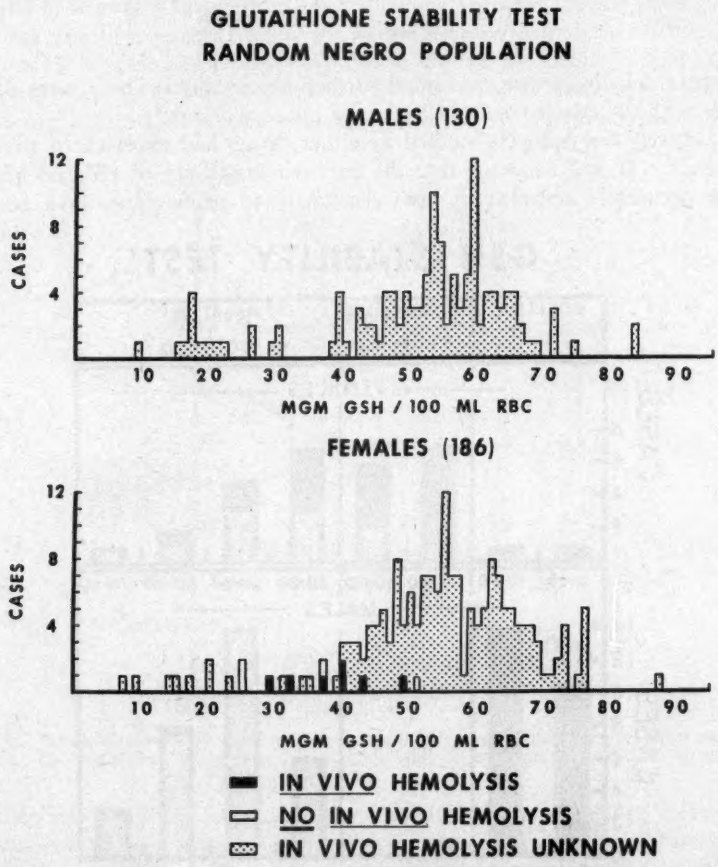

FIG. 3. Distribution of GSH stability test results on a random Negro population. Open squares (no in vivo hemolysis) and black squares (in vivo hemolysis) indicate individuals whose actual response to hemolytic dose of primaquine was tested. Dotted areas represent individuals whose response to primaquine is unknown.

were approximately equal numbers of males and females. In vivo primaquine sensitivity was determined by a clinically safe procedure.[2, 33] In contrast to the results of the glutathione stability test, almost equal numbers of males (11.1%) and females (8.7%) experienced hemolysis (table 2).

* Parke, Davis & Company, Department of Clinical Investigation, Detroit, Michigan.

Results of previous studies based on the vitro glutathione stability test conflicted with our studies based on in vivo hemolysis during primaquine administration. Because of these discrepant results, and the paucity of females in the original standardization of the glutathione stability test, we have attempted to reëvaluate the relationship between in vivo hemolysis and in vitro glutathione instability.

In vivo sensitivity to primaquine was determined either by administration of hemolytic doses of primaquine to inmate volunteers at Stateville Penitentiary, or by small transfusions of chromium 51-labeled erythrocytes from test subjects into compatible normal individuals, who could ingest

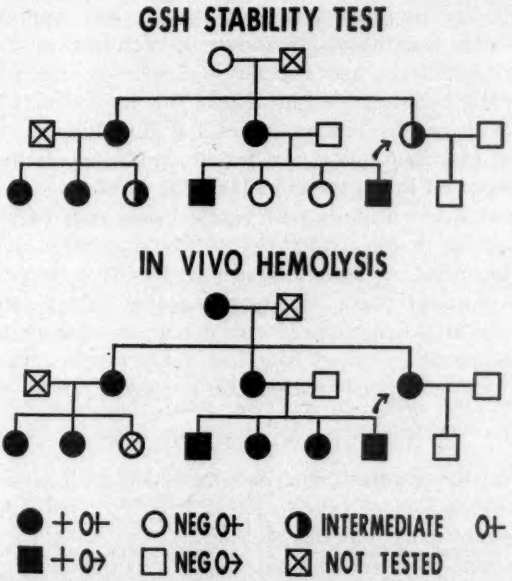

FIG. 4. Comparison of GSH stability test with primaquine-induced hemolysis in a Negro family covering three generations. Similar results have been discovered in other families tested.

primaquine without danger.[2] Hemolysis appears to be an all-or-none phenomenon by our test procedure. The results (figure 2) indicate that the glutathione stability test is reliable in males when all values above 40 mg./100 ml. red blood cells are considered to be normal, and those below 30 mg./100 ml. red blood cells considered to be abnormal. The test frequently gives "intermediate" and even "normal" values in Negro females whose cells are definitely sensitive to primaquine hemolysis. It must be emphasized that cells of "intermediates" that undergo hemolysis are fully as sensitive to primaquine as are the cells of "reactors." However, not all "intermediates" are sensitive.

Our results, employing the glutathione stability test in a study of 316

randomly selected Negroes of unknown sensitivity to primaquine (figure 3), are in general agreement with the findings of Childs and his co-workers. The open and black squares indicate selected individuals whose cells were exposed to primaquine in vivo. Black squares indicate individuals whose cells were thus found to be susceptible to in vivo hemolysis by primaquine, while the open squares represent individuals who demonstrated no in vivo sensitivity. It is concluded that the glutathione stability test is not always reliable for predicting primaquine sensitivity in females.

The large Negro family (figure 4), covering three generations, emphasizes dramatically the divergence of in vivo hemolysis and the in vitro glutathione stability test. Three females who were sensitive to primaquine were undetectible by the glutathione stability test with multiple determinations. The in vitro stability of glutathione is not identical with the phenotype of in vivo hemolysis, and genetic studies employing the glutathione stability test should be interpreted in light of this limitation.

There is a positive correlation between the glutathione stability test and the deficiency of glucose-6-phosphate dehydrogenase in erythrocytes. This has also been reported by Gross and Marks.[32] While it was expected that Negro males and Negro females with marked deficiency of glucose-6-phosphate dehydrogenase in their erythrocytes would undergo acute hemolysis when given primaquine, we have also observed in vivo hemolysis in Negro females whose glucose-6-phosphate dehydrogenase values appear to be almost normal. In vivo hemolysis of cells containing mean normal amounts of glucose-6-phosphate dehydrogenase has not yet been observed, but our studies with Negro females of this type are limited.

Conclusion and Summary

1. In view of the pattern of enzyme abnormalities, it seems worth while to ask: Is it possible for one gene to affect directly or indirectly a variation in the production of more than one enzyme?

2. We conclude that the in vitro instability of reduced glutathione of erythrocytes during incubation with acetylphenylhydrazine is not identical with the phenotype, in vivo hemolysis. Final determination of the mode of genetic transmission of primaquine-sensitive hemolytic anemia must await more definitive genetic and biochemical data.

This study emphasizes the difficulty of choosing the proper phenotype in order to determine the mode of genetic transfer of inherited disease in man.

The importance to physicians of the disorder under discussion is stressed by the fact that this type of acute intravascular hemolysis is frequently an iatrogenically produced disease.

Acknowledgment

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Mukherji. We also wish to acknowledge the advice of Prof. Herluf Strandskov in the genetic studies.

SUMMARIO IN INTERLINGUA

Certe investigatores, usante le test del stabilitate de glutathiona pro determinar le modo de transmission de anemia hemolytic a sensibilitate pro primaquina, ha asserite que il se tracta le plus probabilemente de hereditabilitate per un gen de specificitate sexual con dominantia intermediari. Tamen, le test del stabilitate de glutathiona esseva standardisate super le base de studios in un population de sexo exclusivemente mascule, e le resultatos del test in femininas es frequentemente indeterminate. In plus, nostre studios ha monstrate que le instabilitate in vitro de reducite glutathiona ab erythrocytos, le qual occurre in le curso de incubation con acetylphenylhydrazina, non es identic con lo que occurre in le hemolyse in vivo. Le determination definitive del modo de transmission de anemia hemolytic a sensibilitate pro primaquina debe attender le expansion del currente studios biochimic o le resultatos de experimentos a ingestion de drogas.

Viste le configuration del anormalitates enzymatic in erythrocytos que es sensibile a primaquina, il pare indicate sublevar le question, Es il possibile que un sol gen effectua directemente un variation in le production de plus que un sol enzyma? Le importantia del disordine in question ab le puncto de vista del medico es sublineate per le facto que il se tracta de un typo de acute hemolyse intravascular que es frequentemente iatrogenic.

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THE TREATMENT OF CRYPTOCOCCAL MENINGITIS WITH AMPHOTERICIN B, A NEW FUNGICIDAL AGENT *

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INTRODUCTION

IN recent years there has been a growing medical awareness of the prevalence of chronic systemic fungus infections, many of which are worldwide in distribution.[1] In addition to the more readily apparent cutaneous and osseous infections, deep mycotic infections involving the pulmonary, renal, gastrointestinal and central nervous systems are being reported with increasing frequency.[2] During this time the continuing introduction of potent antibiotics and their enlarging clinical use have resulted in apparent control of many important bacterial infections, with a shifting spectrum of infectious diseases in many communities. As a result of this changing background, chronic fungus infections have appeared to be increasing in prevalence. There are not yet adequate statistical studies to prove whether this phenomenon represents a true increase in significant fungus infections in some communities, or merely a sharpened medical interest in the diagnosis and, more recently, in the treatment of these disorders.

Cryptococcus neoformans is the most frequent cause of mycotic meningitis in man. Since the first reported antemortem diagnosis of central nervous system cryptococcosis in 1914, and its clinical definition in 1916, the disease has been recognized with increasing frequency, especially in the last 20 years.[3, 4] A recent monograph on this subject has pointed out that proportionally more patients with torulosis are reported from hospitals with an increased interest in mycology than from the general hospital population at large.[2] The recent development of amphotericin B, a potent fungicidal agent currently undergoing clinical trial in patients with this and other mycotic infections, has made an early diagnosis of this invading fungus in the central nervous system of vital concern to the patient.[5]

The present paper reports our experience in treating three patients with cryptococcus meningitis at this hospital in the last year and a half. During this time, from a medical service of 150 beds, with some 3,300 admissions per year, four adult patients in this institution were found to have central nervous system cryptococcosis by spinal fluid culture. In this same adult

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patient population there was one case of tuberculous meningitis during this period. The diagnostic and therapeutic implications of this distribution of granulomatous meningitides in this hospital suggest the possible need for a reëvaluation of many hospital patients now receiving isoniazid therapy for presumed tuberculous meningitis.

Case Reports

Case 1. A 56 year old white Kansan, a former lead and zinc miner, was admitted to the University of Kansas Medical Center on April 5, 1956, with headache and weakness of two months' duration. He had noted chronic arthritis of most of his smaller joints for the preceding eight years, and during this time had received an unknown amount of vitamin D therapy by mouth. He had noted symptoms of lower urinary tract obstruction for the preceding year, and was admitted with an indwelling catheter.

Physical examination revealed an afebrile, emaciated, chronically ill male with the characteristic clinical picture of rheumatoid arthritis. Investigation revealed the presence of renal disease with nitrogen retention (blood urea nitrogen, 26 to 39 mg.%), fixed urinary specific gravity of 1.010, and persistent albuminuria, pyuria

Table 1

Cerebrospinal Fluid Findings in Case 1

Date	Initial Pressure mm. H_2O	Cell Count		Sugar Mg. %	Protein Mg. %	Bacteriology
		W.B.C.	R.B.C.			
4–24–56	360	2	49	10	120	+Culture for *C. neoformans* +India ink prep.
4–26–56	320	3	17	13	180	+Culture for *C. neoformans* +India ink prep.

and hematuria, with *Escherichia coli* in the urine by culture. Kidney, ureter and bladder films disclosed multiple calcified deposits in both kidneys and chest roentgenograms disclosed multiple calcified nodules. The patient was negative repeatedly on skin testing with tuberculin, histoplasmin and coccidioidin.

During the third week of hospitalization the patient became more confused, and nuchal rigidity, nystagmus, hyperactive deep tendon reflexes and papilledema appeared. Lumbar puncture revealed an elevated pressure and fluid with the chemical and bacteriologic characteristics shown in table 1. An India ink wet preparation of the spinal fluid demonstrated encapsulated budding yeasts characteristic of *C. neoformans,* later confirmed by culture and mouse inoculation.

On April 24, 1956, the patient was started on amphotericin B,* 500 mg. four times daily by mouth. During the next five days there was a progressive deterioration, with the development of coma, and death five days after starting drug therapy. In that period of time myriads of yeasts of *C. neoformans* were demonstrated in the urine, bronchial secretions and cerebrospinal fluid. No autopsy could be obtained.

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Comment: This 56 year old male undoubtedly had silicosis, from known underground exposure in lead mines for several years in an area with a high prevalence of silicosis among miners. He had nodular lesions in his lungs, with a negative tuberculin skin test, and was excreting a large number of cryptococci in his bronchial secretions. He had rheumatoid arthritis, and had received unknown quantities of vitamin D in the past. He was found to have bilateral renal calcinosis, azotemia, and myriads of cryptococci in his urine. Others have noted the occasional value of urine culture in establishing the diagnosis of systemic cryptococcosis.[2] In this patient the numerous yeasts were initially confused with erythrocytes on examination of the urinary sediment, until India ink preparations demonstrated their true nature. He developed a rapidly progressive picture of meningitis, with deepening coma, and died after five days of treatment with amphotericin B. This drug administered by mouth had no detectable effect on the course of this patient's illness.

Case 2. A 31 year old white housewife, admitted on December 27, 1956, had noted onset of headache, some stiffness of her neck, fever, and vomiting seven months previously. Clinical study at that time revealed the spinal fluid changes recorded in table 2. She was hospitalized for one month and was discharged to her home with the diagnosis of encephalitis. Thereafter she continued to complain of headache, and was reëvaluated at a second hospital four months before admission to Kansas University Medical Center. Studies at that time suggested the presence of a chronic meningitis, with the cerebrospinal fluid changes shown in table 2. During this time all attempts to demonstrate fungi in her cerebrospinal fluid were negative. Therapy for tuberculous meningitis was advised but was later decided against on the basis of the clinical picture, and the suspicion that Torula might be responsible for her symptoms. Following discharge from the second hospital her treatment consisted of repeated spinal taps at biweekly intervals to control chronic headache by reduction in spinal fluid pressure. One week prior to admission to this hospital she noticed some facial numbness and slurring of speech.

Studies performed shortly after admission to Kansas University Medical Center revealed no abnormalities on neurologic examination. Cerebrospinal fluid studies (table 2) confirmed the presence of a chronic meningitis. *C. neoformans* was isolated from the cerebrospinal fluid by culture and India ink preparations shortly after admission, and she was started on amphotericin B therapy. Initially she received 50 mg. of this drug in 1,000 ml. of 5% dextrose in water by slow intravenous drip daily for two weeks. Following this she was placed on 100 mg. every other day by a similar method of administration for the next eight weeks. On April 13 she was started on oral amphotericin B, 4 gm. daily in divided doses, and was discharged to her home one week later. She continued to take the oral drug for two more months, at which time our supply of oral medication was exhausted, and all therapy was then discontinued.

The patient's headache ceased after one month of therapy, and she appeared to be free of disease. Her cerebrospinal fluid (table 2) became normal after three months of treatment, and has remained so. At no time during her course was there any evidence of major toxicity to hematopoietic, hepatic, renal or central nervous systems that could be attributed to the use of amphotericin B. The only side-effect noted from use of this drug was the development of a chemical thrombophlebitis when the rate of infusion became too rapid. After one pyrogenic reaction with

phlebitis early in her course, the infusion was spaced over a seven-hour period without any detectable toxicity.

Comment: This 31 year old housewife had chronic Torula meningitis of seven months' duration when drug therapy was started. No portal of entry for the fungus or extracerebral focus of the disease was demonstrated.

TABLE 2

Cerebrospinal Fluid Findings in Case 2

	Date	Initial Pressure mm. H_2O	Cell Count		Sugar Mg. %	Protein Mg. %	Bacteriology *C. neoformans*	Amphotericin B Therapy
			W.B.C. Pmn. | Lym.	R.B.C.				
Out-Patient	5-19-56	340	189 / 6 | 183	0	58	74	Neg.	
	6-12-56		233 / 13 | 220	0	—	105	Neg.	
	10-10-56	320	220 / 10 | 210	0	25	75	Neg.	
K.U.M.C.	12-28-56	290	120 / 4 | 116	0	29	114	+India ink +Culture +Mouse inoc.	*I.V.* 50 mg.O.D. (2 wks.)
	1-24-57	250	29 / 0 | 29	15	46	72	Neg.	
	2-14-57	330	14 / 0 | 14	20	56	59	Neg.	*I.V.* 100 mg. q.O.D. (8 wks.)
	3-14-57	300	13 / 0 | 13	1	43	54	Neg.	*Oral* 6 gm. O.D. (8 wks.)
Out-Patient	4-27-57	160	6 / 0 | 6	1	43	50	Neg.	↓
	5-25-57	170	1 / | 1	12	48	35	Neg.	Stop
	7-27-57	130	0	1	65	41	Neg.	
	9-28-57	126	0	11	48	34	Neg.	
	11-23-57	120	2 / | 2	1	38	34	Neg.	

After one month of intravenous drug therapy her headache cleared, and after three months of treatment her cerebrospinal fluid became normal and has remained so. She is now being closely followed, and has shown no evidence of recurrence of infection in the nine months since the drug was discontinued. She has returned to her previous job as a medical secretary.

Case 3. A 45 year old Negro, a former meat packer, was re-admitted on March 25, 1957, for treatment of chronic Torula meningitis with amphotericin B. This man's illness had started in 1946 with severe chronic headache. He was studied in

two different hospitals during that year without establishment of a definite diagnosis. It was noted that he had papilledema and clinical evidence of meningitis. Spinal fluid changes during the past 11 years are shown in table 3. He had a temporary period of left hemiparesis in 1946, but recovered sufficiently to return to work as a meat cutter despite residual spasticity of the left leg. He was able to work until late in 1948 despite progressive "weakness" of both lower extremities and the development of urinary incontinence. At the time of his first admission to this hospital, in May, 1949, he was unable to walk. Examination revealed marked spasticity of both legs, with bilateral Babinski reflexes. The left arm also showed hyperactive reflexes. Sensory examination was normal, and no cranial nerve abnormalities were noted. Chest roentgenograms at that time disclosed a widespread pulmonary lesion with cavity in the right upper lobe. Sputum examination revealed *Mycobacterium tuberculosis* by culture, and the presumptive diagnosis of chronic active pulmonary tuberculosis with tuberculous meningitis was made. Cerebrospinal fluid changes in 1949 are seen in table 3. Daily dihydrostreptomycin in 1 gm. dosage was given for two months, and during this time some improvement was noted in his clinical picture. Culture of cerebrospinal fluid shortly after admission yielded an encapsulated budding yeast identified as *C. neoformans*. At no time was *M. tuberculosis* recovered from the cerebrospinal fluid culture. Table 3 also summarizes chemotherapy administered for active pulmonary tuberculosis and cryptococcosis during the 27 months he was hospitalized. Acti-dione in a daily dose of between 10 and 20 mg. was given for three weeks in August, 1949, but was discontinued because of nausea and vomiting. However, the latter complaints persisted for two months following withdrawal of Acti-dione. He received Tibione (4-acetyl-amino-benzal thiosemicarbasone), 150 mg. daily, from June, 1950, to April, 1951. His sputum was last culture-positive for tubercle bacilli in April, 1950.

On prolonged rest and Tibione therapy the patient's chest roentgenograms became stable, and on discharge in the summer of 1951 his pulmonary tuberculosis had reached the inactive stage. By December, 1950, the symptoms of meningitis had regressed despite the persistence of abnormalities in the cerebrospinal fluid, and rehabilitation for the residual paraplegia was started. By use of a walking frame he was discharged to his home in August, 1954, with the cerebrospinal fluid still abnormal. The last positive culture of the spinal fluid for *C. neoformans* at that time was in February, 1950.

During the next five years there was little change in this clinical picture. The patient maintained a left spastic hemiparesis, with weakness of the right leg, that required the use of a walking frame. Cerebrospinal fluid examination (table 3) continued to reflect activity of the smoldering infection, and he was re-admitted in July, 1956, for further study. Spinal fluid at that time was again positive for *C. neoformans* following intracerebral mouse inoculation. Pulmonary tuberculosis was felt to be inactive at that time, and numerous gastric cultures were negative both for *M. tuberculosis* and Torula. Nine days later the patient was discharged, and on August 1, 1956, he was started on a regimen of oral Daraprim* (pyrimethamine), an antimalarial nucleic acid antagonist, 50 mg. daily, with sulfadiazine, 4 gm. daily by mouth. This regimen was based on the report by Renzetti and Feldman[2] of successful treatment of a patient with coexistent systemic cryptococcosis and pulmonary tuberculosis, and success in the use of this nucleic acid antagonist in the treatment of experimental and clinical toxoplasmosis.[6] It is of interest that the patient reported by Renzetti and Feldman also received streptomycin and isoniazid to control active pulmonary tuberculosis. In that patient, there was no apparent central nervous system involvement by the fungus, and skin biopsy still contained crypto-

*Generously supplied by Burroughs-Wellcome Co., Inc., Tuckahoe, N. Y.

TABLE 3

Summary of Cerebrospinal Fluid Changes, Case 3

	Date	Initial Pressure mm. H_2O	Cell Count		Sugar Mg. %	Protein Mg. %	Bacteriology *C. neoformans*	Drug Therapy
			W.B.C. % Pmn. | Lym.	R.B.C.				
Other Hospitals	1-30-46		640 4 | 96		30	120	—	
	2- 9-46		— —		54	116	—	
K.U.M.C.	5-17-49		58 84 | 16	412	22	126	+India ink +Culture	
	10-13-49	100	51 74 | 26	0	30	350	+Culture	Acti-dione 10 mg. O.D. (3 wks.) August 1949
	2- 8-50	120	32 36 | 64	0	18	360	+Culture	Tibione 150 mg. O.D. (10 months) June 1950–April 1951
	2- 8-51	160	49 32 | 68	500	17	435	Neg.	
	7-16-51	200	70 34 | 66	69	18	255	Neg.	
Out-Patient	5- 1-56	180	58 24 | 76	0	19	285	+Mouse inoculation	
K.U.M.C.	7-18-56	190	22 45 | 55	23	16	260	Neg.	Daraprim 50 mg. O.D. (8 wks.) 25 mg. O.D. (4 wks.) Sulfadiazine 4 mg. O.D. (12 wks.)
Out-Patient	11- 7-56	170	222 72 | 28	0	13	233	Neg.	
K.U.M.C.	3-22-57	78	128 40 | 60	0	22	550	Neg.	Amphotericin B 3 gm. O.D. (oral) (2 wks.)
	4-16-57	112	72 32 | 68	2	15	500	+Culture	20 mg. O.D. (I.M.) (1 wk.)
	6-11-57	130	17 0 | 100	8	39	182	Neg.	100 mg. q.O.D. (I.V.) (3 mos.)
	7-10-57	216	29 0 | 100	0	50	195	Neg.	
	8- 1-57	160	237 18 | 82	18	40	300	Neg.	Intrathecal 1 mg. q.O.D. × 5 ↓ Stop
	8-12-57	210	57 35 | 65	3	27	500	Neg.	
	9-11-57	156	8 0 | 100	0	36	160	Neg.	
	10-21-57	136	8 0 | 100	11	41	133	Neg.	
	11-21-57	140	30 25 | 75	3	29	140		

cocci after five months of combined drug treatment. Thereafter no yeasts could be demonstrated, and the patient was judged to be clinically cured of both infections.

During subsequent weeks of Daraprim-sulfadiazine therapy, difficulty was experienced in following this paraplegic by weekly blood counts in the outpatient department, and he failed to return for adequate supervision. By the end of three months of chemotherapy, epistaxis occurred, and he was re-admitted with severe neutropenia, thrombocytopenia and anemia. Table 4 records the toxic hematologic picture of "marrow-arrest" produced by this regimen. Further studies suggested that this bone marrow depression was secondary to Daraprim, which had been discontinued a few days prior to admission. Treatment with leucovorin, ACTH, cortisone and other supportive measures resulted in a prompt recovery of normal marrow elements in subsequent weeks, as seen in table 4. Steroids were gradually withdrawn thereafter, and the patient was discharged to his home some two weeks after admission on antituberculosis chemotherapy consisting of isoniazid, 300 mg. daily. During this time gastric cultures were negative for *M. tuberculosis*, and chest roent-

TABLE 4

Hematologic Changes Associated with Daraprim-Sulfadiazine Therapy, Case 3

Date	Peripheral Blood Studies								Bone Marrow	Drug Therapy
	Hgb. Gm.	W.B.C.	Pmn.	Fil. Pmn.	Lym.	Eos.	Mon.	Platelets		
7-18-56	16	9,500	69	69	25	1	5		7-24-56 Normal	↑Daraprim—50 mg. O.D. Sulfadiazine—4 gm. O.D. from 7-31-56 ↓to 9-17-56
8-28-56	13.5	2,150	46	45	57	7		139,000		
9-25-56	11.0	8,850	76	76	14	2	7	372,000		
10-11-56	12.4	8,150	78	78	14	2	4	236,000		↑Daraprim—25 mg. O.D. Sulfadiazine—4 gm. O.D. $NaHCO_3$—4 gm. O.D. ↓from 9-30-56 to 10-29-56
10-16-56	11.3	3,850	62	62	30	7	1	165,000		
										10-30-56
10-30-56	9	1,200	25	25	66	8	1	30,000		↑ACTH—20 U.I.M. (Gel.) Cortisone—100 mg. O.D. Leucovorin—3 mg. t.i.d. Crude Liver Brewers Yeast ↓ 11-8-56
11- 1-56	9.3	1,250	43	37	41	3	13	15,000	11-1-56	
11- 3-56	10.5	11,700	70	45	5	2	8	30,000	Hyperplasia,	
11- 5-56	10.2	28,000	67	59	21	4	8	65,000	with marked	
11- 7-56	10	23,800	63	55	23	4	2	82,000	left shift.	
11-10-56	11	23,350	76	76	17	5	2	302,000	Numerous	
11-13-56	10	17,450	68	68	24	5	3	393,000	myelocytes	
12-18-56	13.2	5,900	61	61	32	2	5	228,000	are present	
4-26-57	13	9,100	84	84	13		3	218,000		

genograms remained stable in appearance. Through all of this there was no appreciable change in the patient's clinical condition or in the cerebrospinal fluid findings.

During the next four months the patient did well. He remained afebrile, receiving physiotherapy biweekly with no apparent change in the residual paralysis. He was re-admitted in March, 1957, for a trial of amphotericin B therapy. Isoniazid therapy was discontinued at that time. Amphotericin B was initially given in the oral form for two weeks, without appreciable alteration in the spinal fluid findings. At the end of two weeks of treatment he still had a positive cerebrospinal fluid culture for *C. neoformans*. Next, an intramuscular preparation of this drug was administered for one week to study blood and cerebrospinal fluid drug levels. Following this the patient received 100 mg. of amphotericin B every other day intravenously for the next three months. As seen in table 3, there was a gradual improvement in the cerebrospinal fluid during this period of time. Intravenous therapy was administered with extreme difficulty because of inadequate veins and the development of thrombophlebitis during this period of time. After approximately four months of drug therapy by all routes, amphotericin B was given intrathecally in a dosage of

1 mg. every other day for five administrations. Following this, all drug was discontinued and he was observed for another month in the hospital. As was anticipated, intrathecal amphotericin B caused a rather marked systemic and local reaction, with fever, headache, malaise, and alterations in the spinal fluid (table 3). This simulated the clinical picture observed following intrathecal tuberculin therapy of tuberculous meningitis.[7] These findings regressed promptly in the week following intrathecal drug therapy, and at the time of discharge in September the patient was again feeling well. In the four months that he has been followed as an outpatient since stopping drug treatment little change has been noted in the cerebrospinal fluid. At the present time he appears to have reached a fairly stable picture of chronic active meningitis. All spinal fluids obtained since the start of amphotericin B therapy have been sterile for fungi.

Comment: This 45 year old Negro male has had a chronic central nervous system infection, presumably cryptococcosis, for the last 11 years. During this time he also developed active pulmonary tuberculosis, which has been treated to the state of inactive disease. Cerebrospinal fluid has been positive by culture for *C. neoformans* for the last eight years. Despite the chronicity of this disease, it is of interest that amphotericin B was effective in restoring the cerebrospinal fluid to a more nearly normal pattern and in sterilizing it, thus far, for fungi. During this period of observation there has been no alteration in the residual neurologic picture, which must be presumed to be secondary to permanent neural damage, with resultant meningeal fibrosis.

Discussion

The isolation, physical and chemical characteristics, and pharmacologic properties of amphotericin B have been described.[8, 9] This antibiotic has been previously reported to be of value in the treatment of central nervous system cryptococcosis.[11] Our experience with this drug in the three patients being reported, as well as in others previously described, documents its definite therapeutic value in Torula meningitis when administered early enough in the course of this illness.[12] Its broad fungicidal action against *C. albicans, H. capsulatum, C. immitis* and *B. dermatitidis* has been demonstrated both experimentally and clinically.[5, 10]

We have noted no untoward reactions of significance to this drug when it was prepared and administered as directed by the manufacturer. Acute side reactions, including shaking chills with fever, may occur on occasion with the initial infusion. These can be minimized or eliminated by premedication with aspirin or an antihistamine preparation. In its present form, amphotericin B must be adequately diluted in water (1 mg./10 ml.) and administered by slow intravenous drip over a span of several hours. Any attempt to hasten the infusion resulted in a pyrogenic reaction and a local chemical thrombophlebitis. Total daily dosage should be increased slowly up to 1 mg. per kilogram of body weight. Transient elevation of the blood urea nitrogen has been noted with higher doses of the drug, but to date no significant toxic changes in the hematopoietic, hepatic, renal, cutane-

ous or nervous systems have been observed in our patients, one of whom received the drug for four months. However, continued study of renal and hepatic function during prolonged courses of drug therapy remains necessary until a greater clinical experience has been accumulated.

The optimal dosage and duration of amphotericin B therapy for human central nervous system cryptococcosis must await further clinical study. It would appear logical that in the treatment of a chronic and often diffuse granulomatous meningeal infection, prolonged parenteral therapy to ensure an adequate cerebrospinal fluid penetration of the drug would be necessary. In vitro studies have shown the minimal inhibitory concentration of amphotericin B for *C. neoformans* to be a fraction of 1 μg. per milliliter of broth.[8] Blood level determinations in our laboratory have shown that adequate fungicidal concentrations of this drug are attained on the above regimen of intravenous therapy and persist for as long as 18 hours thereafter. For this reason, infusion of the drug on alternate days is possible where a higher dosage is being used.

Cerebrospinal fluid levels of amphotericin B following intravenous administration have not been consistently demonstrable by us utilizing the bio-assay technic suggested by Littman.[13] Following intrathecal drug administration, detectable cerebrospinal fluid levels have been shown to persist for up to 48 hours. The apparent recovery of case 2 without the use of intrathecal amphotericin B suggests that adequate fungicidal drug levels were reached in the cerebrospinal fluid, even though present methods of detection by bio-assay failed to demonstrate their presence.

We have on occasion noted great difficulty in differential diagnosis, including cerebrospinal fluid changes, between cryptococcal and tuberculous meningitis, and meningeal carcinomatosis. In former years, when no therapy existed for any of these diseases, there was little to do but await the deciding report of a cerebrospinal fluid culture or autopsy, since all were invariably fatal conditions. But with the striking reduction in mortality from tuberculous meningitis since the advent of streptomycin and isoniazid therapy, an early diagnosis of this disease is of greatest aid in successful therapy.[14] The addition of amphotericin B to our armamentarium now makes an early differentiation between mycobacterial and fungal meningitis of extreme importance to the patient. It is hoped that further study will produce an efficient and rapid method of differentiating mycotic meningitis from mycobacterial meningitis. Study of the cerebrospinal fluid, utilizing known metabolic differences between yeasts and bacteria, and their end-products of metabolism, may greatly aid in the future differential diagnosis of granulomatous meningitis, and speed the administration of specific therapy.

Summary

Amphotericin B has proved to be an effective and practical drug for the treatment of cryptococcal meningitis. Blood and cerebrospinal fluid levels

of this drug have been found to be of low order by biologic assay technic. The elimination of *C. neoformans* from the spinal fluid of two patients is described.

SUMMARIO IN INTERLINGUA

Cryptococcus neoformans es le plus frequente causa de meningitis mycotic in humanos. In le curso del passate 20 annos, iste disordine ha essite reportate con crescente frequentias ab omne partes del mundo. Usque nunc le tractamento de iste chronic infection systemic ha remanite generalmente non-satisfactori. Le recente introduction, in usos clinic, de amphotericina B—que es un potente antibiotico fungicida derivate ab un streptomycete—ha stimulate un nove optimismo con respecto al possibilitate de tractar iste infection a bon successo. Le droga se ha provate clinicamente efficace in le tractamento de patientes qui albergava *Candida albicans, Histoplasma capsulatum, Coccidioides immitis,* e *Blastomyces dermatididis.*

Tres patientes con cryptococcosis del systema nervose central esseva tractate con amphotericina B. Le prime recipeva le droga per via oral durante cinque dies. Ille moriva sin beneficio apparente. Le duo proxime patientes monstrava melioration. Le un de illes habeva symptomas de un infection chronic del systema nervose central de un duration de septe menses ante le initiation del tractamento drogal. Le administration intravenose de amphotericina B durante 10 septimanas resultava in le retorno del fluido cerebro-spinal a un stato normal. Le re-examine del patiente un anno post le cessation del administration de amphotericina B non revelava ulle stigma de un infection residue.

Le tertie patiente, paraplegic ab 10 annos de non-tractate torulosis del systema nervose central, ha monstrate melioration in le stato del fluido cerebro-spinal e in su condition clinic. Ille continua exhibir signos de un latente infection del systema nervose central, ben que il ha devenite impossibile isolar le fungo ab le fluido spinal.

Investigationes del nivellos de amphotericina B in le sanguine e in le fluido cerebrospinal ha monstrate que iste droga possede un periodo prolongate de activitate post su administration intravenose. Le penetration del barriera meningee es de basse magnitude, a judicar per le multo micre quantitates del droga que pote esser detegite in bio-essayos de fluido cerebro-spinal.

Le resultatos del tractamento in iste micre gruppo de patientes es incoragiante. Amphotericina B merita esser evalutate additionalmente in le tractamento de meningitis cryptococcal.

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COMPLETE HEART BLOCK: A FOLLOW-UP STUDY*

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IN 1936 Graybiel and White [1] analyzed the clinical data in 72 patients with complete heart block seen at the Massachusetts General Hospital up to that date. Recently Penton, Miller and Levine [2] have detailed their experience in 251 office and hospital patients with the same disorder. The purpose of the present publication is to expand the original series of Graybiel and White with experience through the year 1955, for comparison with the similar group of Penton et al., with particular emphasis on the clinical features, nature of the underlying heart disease, and the ultimate outcome of the patients.

A review of the 160,000 electrocardiograms taken at the Massachusetts General Hospital from 1925 to 1955, inclusive, revealed 350 patients who showed complete atrioventricular dissociation on one or more tracings. The majority had been hospitalized on the wards or the private services during this period, and the remainder were from the office practice of cardiologists associated with the hospital. Adequate clinical records were available in 278 cases, and this report is based on these patients, in 191 of whom there was knowledge of their state of health in 1955, or confirmation of death in the form of hospital record, death certificate or autopsy report.

Selection was limited to those patients with electrocardiograms showing complete atrioventricular dissociation where the ventricular rates were slower than the atrial (generally under 50, with the exception of some patients with congenital heart block or digitalis intoxication, who had ventricular rates up to 75 or more on occasion). Instances of partial heart block or complete dissociation with rapid ventricular rates have been excluded.

There were 174 males and 104 females. In the coronary and rheumatic groups males predominated about two to one. In the cases with congenital heart block and in those with digitalis intoxication there was an equal incidence of male and female.

Survival data have been determined only from those patients known to have died. While this may introduce an unfavorable bias, the number of patients still living in 1955 is small.

CONDITIONS ASSOCIATED WITH HEART BLOCK

Coronary Heart Disease Without Hypertension or Acute Infarction: Ninety-six patients (35%) gave a history of angina pectoris, previous

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TABLE 1

Etiologic Factors in Series of Cases with Complete Heart Block

	Number	Per Cent	
Coronary heart disease alone	96	35	
Coronary heart disease with acute infarction	38	14	73
Coronary heart disease and hypertension, or hypertensive heart disease	68	24	
Rheumatic heart disease	23	8	
Digitalis intoxication	16	6	
Congenital	17	6	27
Miscellaneous	11	4	
Unknown	9	3	
	278	100	

myocardial infarction, or both. There were 65 men and 31 women in this group. The women first developed block at a slightly later age than the men (a two-year difference), and their survival time after onset was slightly longer (table 2). The mean age at onset for the group as a whole was 67.1 years; the mean age of death was 71.1 years; the mean survival was four years. This compares with an expected survival of about 13 years for normal individuals of age 65, and of about seven and a half years for individuals developing angina pectoris at the same age.[3]

Over 90% of this group remained in complete heart block from its onset, although some required a few weeks for the block to become established. Half of the patients (47) had one or more Adams-Stokes attacks. Thirty-eight patients were in congestive failure of varying degrees of severity, but in no case was failure precipitated or significantly aggravated by the development of block.

Eleven of the men and 13 of the women were hypertensive, and two men and four women were diabetic.

Seventeen of the patients with coronary heart disease remained in complete block for more than five years, and seven for more than 10 years.

TABLE 2

Survival Time after Onset of Complete Heart Block

	Age Onset	Age Death	Survival (mos.)
Coronary heart disease alone, total	67.1	71.1	48
Male	66.5	70.3	45
Female	68.5	73.0	54
Coronary heart disease with acute infarction, total	65.3	66.5	13
Male	64.6	65.3	8
Female	66.6	68.6	24
Coronary heart disease with hypertension, total	67.0	71.7	55
Male	67.3	72.5	62
Female	66.6	70.0	41
Rheumatic heart disease, total	43.3	50.4	85

One man developed block with frequent Adams-Stokes attacks at the age of 67, but had no further syncope after a year and remained in complete block until his death at 84, 17 years later.

The average pulse rate of this group at the time of first observation with block was 38. The blood pressure showed a mean systolic pressure of 158 mm. of mercury and a mean diastolic of 75 mm. of mercury (pulse pressure, 83 mm. of mercury).

Acute Myocardial Infarction: Thirty-eight patients (14%), 26 men and 12 women, developed complete heart block during the early days of acute myocardial infarction. Among the men the mean age at onset was 64.6 years, and the mean age at death 65.3 years (eight-month survival); 12 died within a month of the acute episode. Among the women the age at onset was 66.6 years, and the age at death 68.6 years (two-year survival); four died within a month of the acute infarction.

Among those cases in which the location of the infarct could be determined from the tracing, there were 15 with posterior, six with anterior, and one with subendocardial infarction.

One man and four women were diabetic, and six men and six women were hypertensive.

The block in this group with acute myocardial infarction was usually transient. In 31 of the 38 cases it lasted less than a month. In those patients surviving a month or more after the infarction the block lasted from three to 36 months, terminating either spontaneously or with the death of the patient. One patient remained in complete heart block until his death 36 months after infarction, and another reverted to normal rhythm 36 months after her infarction and the onset of block. Only three of the men and four of the women experienced Adams-Stokes attacks.

The mean pulse rate in these cases was somewhat higher (45), and the blood pressure (140 mm. of mercury systolic, 80 mm. diastolic) and pulse pressure (60 mm. of mercury) somewhat lower than in those patients with coronary heart disease without infarction.

Hypertension: Sixty-eight patients (24%), 41 men and 27 women, had established hypertension (over 170 mm. of mercury systolic and 100 mm. diastolic), without angina pectoris or previous myocardial infarction, prior to the onset of complete heart block. However, coronary atherosclerosis was doubtless responsible for the damage to the conduction tissue in these patients.

The survival after onset for males was 5.2 years (mean age at onset, 67.3 years; mean age at death, 72.5 years), contrasted with a 3.4 year survival for females (onset, 66.6 years; death, 70 years). In almost all cases the block was permanent from the time of onset or after a brief period of transient episodes.

One man and two women were diabetic. Nineteen men and 11 women, slightly less than half the group, had one or more Adams-Stokes attacks.

The mean pulse rate was 40, and the blood pressure values were 210 mm. of mercury systolic and 90 mm. diastolic (pulse pressure, 120 mm. of mercury).

Seventeen of the hypertensive group survived over five years from onset, and five lived more than 10 years. The longest recorded survival was 20 years, in a man who developed block at 65 and died at 85; he had only minor spells of dizziness and weakness during this time.

Rheumatic Heart Disease: Twenty-three patients (8%) had rheumatic heart disease. Seventeen were male and six were female. Various valvular lesions were present: five cases had mitral stenosis; two, mitral insufficiency; two, aortic stenosis; two, aortic insufficiency; two, mitral stenosis and insufficiency; five, combined mitral and aortic lesions; two, aortic stenosis and insufficiency. In the remaining three patients the exact valve lesions were not specified.

The mean age at onset was 43.3 years, and the mean age at death was 50.4 years. Seven patients first developed complete block in their forties, and another six after the age of 50. In these patients rheumatic heart disease may not have been the sole cause of block, and in several instances severe coronary atherosclerosis was found at autopsy. Only 12 had been taking digitalis. Five were hypertensive.

Seven patients had Adams-Stokes attacks during their course, but their survival time exceeded that of the others and in no instance was death related to an Adams-Stokes attack.

In all but one case the block was permanent, and in this patient it was intermittent over a period of many years. In one patient complete block was believed to have existed without change for 22 years, but this case lacked adequate documentation. The longest proved duration of block among rheumatic patients was 17 years, found in a man who developed it at 31 years of age with a few Adams-Stokes attacks, and was living with complete heart block but without symptoms from his rheumatic heart disease or block at the age of 48.

In this group the mean pulse rate was 45, and the mean blood pressure 148 mm. of mercury systolic and 72 mm. diastolic (mean pulse pressure, 76 mm. of mercury).

Congenital Heart Block: Seventeen patients (6%) were considered to have congenital heart block. There were nine males and eight females. Five of the males and four of the females showed evidence of an associated ventricular septal defect. One patient had a degenerative disease of the basal ganglia, and one was a Mongolian idiot.

One patient gave a history of diphtheria in childhood, but a slow pulse had been recorded before that illness.

Syncopal attacks were unusual. Four patients had experienced one brief episode of syncope in childhood, associated with fever or exercise. One girl of 14 had had several Adams-Stokes attacks within a few days without

recurrence; she was believed to have congenital heart block. Five other patients had complained at times of slight weakness or dizziness. The rest were without symptoms and were living normal lives. Three had enlargement of the heart.

The mean pulse rate was 48, but on exercise it often rose to rates between 60 and 100. The mean blood pressure values were 132 mm. of mercury systolic and 63 mm. diastolic (mean pulse pressure of 69 mm. of mercury).

One patient with suspected congenital heart block and without other signs of heart disease died at 79, but autopsy was not performed. Another, a woman of 65, has been carefully followed for 40 years and is free of symptoms except for those of mild neurocirculatory asthenia.

Digitalis: In 16 patients (6%) the onset of block was definitely or probably related to excessive administration of digitalis. With the exception of two patients with rheumatic heart disease and one healthy girl of seven, all were over the age of 50, and had coronary or hypertensive heart disease and eight were over 70. There were eight males and eight females.

In all but five instances the block lasted less than two weeks, and in six cases it was probably related to the death of the patient. Only three of these patients with digitalis-induced block experienced Adams-Stokes attacks.

The child of seven who showed complete heart block had no heart disease. She had been taking thyroid extract three times daily, and through error her prescription was refilled with digitoxin, 0.15 mg. tablets. She took three tablets daily for three or four days but then developed such nausea and vomiting that she was unable to continue the medicine. The vomiting persisted for four more days, at the end of which time she was brought to the hospital. She was found to have complete heart block, with a ventricular rate of 55, but no dizziness or weakness despite the protracted vomiting. During the next week the complete block changed to partial block (first 2:1 and then a prolonged P-R interval), and finally cleared completely.

The mean pulse rate in this group was 49, the blood pressure 130 mm. of mercury systolic and 70 mm. of mercury diastolic (mean pulse pressure, 60 mm. of mercury).

Miscellaneous: Eleven patients developed heart block in association with less common types of heart disease. Two, already mentioned, were caused by diphtheritic myocarditis.

There were two instances of primary amyloidosis of the heart. In one of these, a woman of 68, complete heart block existed for only one day before death in severe congestive failure, and was associated with digitalis administration, which may have played the greater role. In the other, a man of 68, complete block existed for a month prior to death in congestive failure; autopsy showed amyloidosis of the heart.

Three patients developed block in the course of a rapidly progressive fatal myocarditis of unknown etiology, confirmed in each case by autopsy. In a man of 45 it lasted 12 months, until death; in a woman of 54 it lasted six months, until death; in a woman of 22 it lasted four months, until death.

One girl, now eight years old, has had complete block since the age of six, with a greatly enlarged heart but no murmurs; she is suspected of having endocardial fibroelastosis.

A man of 22 died after six months of severe congestive failure and complete heart block and was found to have idiopathic hypertrophy of the heart.

A man of 64 with carcinoma of the lung and complete heart block of six months' duration was found to have metastatic involvement of the pericardium and myocardium.

In nine patients it was not possible to establish the nature of the underlying heart disease.

Other Features

Adams-Stokes Attacks: One hundred five patients (38% of the total series) had experienced loss of consciousness or convulsions or both during the course of their heart block. These symptoms were usually recurrent over a period of days to months. The patients with Adams-Stokes attacks in most instances remained in complete heart block once it became established, for the rest of their lives, while those without Adams-Stokes attacks more often reverted to normal sinus rhythm. The groups with the highest incidence of transient block (those with acute myocardial infarction and those showing excessive digitalis effect) seldom suffered from either syncope or convulsions.

Syncope seldom occurred without ventricular standstill or fibrillation of at least 10 to 15 seconds' duration. Even elderly patients were often able to tolerate pulse rates in the twenties without syncope when ambulatory, and in several instances remained fully conscious while lying in bed with pulse rates between five and 10.

The prognosis of the Adams-Stokes syndrome due to complete heart block is more hopeful than is usually appreciated. Although 23 of the 105 patients with this complication died within two weeks of its onset, nevertheless only seven died as the direct result of their ventricular standstill or tachycardia with syncope. Nine other patients succumbed from the effect of recent myocardial infarction, and the remaining seven from causes other than asystole. From the end of the second week to the end of the second year after onset, 19 additional patients died, five during documented Adams-Stokes attacks and six with sudden exitus; in the remaining eight the cause of death was unrelated to heart block.

In the whole series and in each of the groups individually the mean survival time of patients with Adams-Stokes attacks exceeded that of patients not so afflicted. Although these data were determined from those

patients who had died, the proportion of patients with Adams-Stokes attacks was identical in the survivors and in the deceased group. In the series as a whole it so happened that patients with syncope or convulsions lived more than twice as long from the onset of block (72 months) as did those without these symptoms (31 months). This favorable association was most striking in the group with angina pectoris or previous myocardial infarction, but was found in all groups (table 3). Although it was first

TABLE 3

Relationship of Adams-Stokes Attacks to Survival Time

	Survival Time in Months	
	With Adams-Stokes Attacks	Without
Coronary heart disease	75	18
Coronary heart disease with acute infarction	45	9
Coronary heart disease with hypertension	63	47
Rheumatic heart disease	96	79
Entire series	72	31

thought that this was due to the fact that patients with Adams-Stokes attacks come to medical attention earlier in the course of the disease, their mean age was less than nine months greater than that of patients without Adams-Stokes attacks, and this does not appear to be the explanation.

A little more than one third of the patients complained of lesser symptoms alone, particularly of transient spells of weakness and dizziness, or a lasting feeling of fatigue. At least a quarter of the series had no significant symptoms related to the block at any time.

TABLE 4

Miscellaneous Relationships in Complete Heart Block

	Total Number	History of Diphtheria	History of Syphilis	Heart Failure	Enlarged Heart	Adams-Stokes Attacks	Mean Pulse	Mean Blood Pressure
Coronary heart disease	96	5	1	38	80	47	38	158/75
Acute infarction	38	1	1	12	30	7	45	140/80
Hypertension	68	4	5	21	58	30	40	210/90
Rheumatic heart disease	23	2	0	9	21	7	45	148/72
Digitalis intoxication	16	0	0	12	16	3	49	130/70
Congenital heart disease	17	1	0	1	4	4	48	132/63
Miscellaneous	11	2	1	6	10	4		
Unknown	9	2	0	1	7	3		
	278	17	8	100	226	105		

Hypertension, Heart Failure, Cardiac Enlargement: One hundred twelve patients (40%) had blood pressures over 170 mm. of mercury systolic and 100 mm. of mercury diastolic recorded on one or more occasions prior to the onset of block. One hundred patients (36%) had some degree of heart failure. Two hundred twenty-six patients (80%) had enlarged hearts.

Pulse Pressure: A compensatory rise in systolic and a drop in diastolic pressure with the onset of a slow ventricular rate were noted in most pa-

tients, the amount of the resulting pulse pressure varying from group to group (table 4).

History of Diphtheria: Seventeen patients gave a history of diphtheria in childhood, but in only two of them could the onset of block be related directly to that illness. One boy had repeated episodes of syncope and convulsions lasting several months immediately following diphtheria at the age of 10. He then became symptom-free until he was 36, at which time complete heart block developed and was permanent until his death at 45. The other patient is a woman who has had complete heart block since a severe episode of diphtheria at the age of six. She has never had symptoms related to the block, and carries on an active life at the age of 50. Ten of the other patients with a history of diphtheria developed block late in life in association with hypertension or with coronary heart disease, and two others in association with rheumatic heart disease.

History of Syphilis: In nine patients there was a history of primary syphilis or a positive serologic reaction, or both. Most of them received treatment early in the course of the disease, and eight had no subsequent signs of syphilitic heart disease. One patient had a soft aortic systolic murmur, an aortic diastolic murmur, and a history of angina pectoris. His heart disease was considered to be due primarily to coronary atherosclerosis, as was thought to be the case in the other eight patients.

Treatment

Various medications were administered to these patients to prevent or relieve asystole, or to increase the idioventricular rate to the level at which symptoms would disappear. The sympathomimetic amines (epinephrine, ephedrine or Isuprel) were most commonly used. Other preparations included thyroid extract, atropine, Paredrine, belladonna, barium chloride and aminophylline. In addition to the 16 patients in whom block was caused by digitalis, this drug was given to 103 patients when required for heart failure, without adverse effect on already established complete heart block; it sometimes produced complete block from previous partial block. Intravenous sodium lactate was given to one patient without effect. Quinidine and Pronestyl were used for episodes of ventricular tachycardia. The electrical cardiac pacemaker has been used helpfully in some patients with repeated Adams-Stokes attacks, but it was not employed in this series. In general, the most successful drugs in relieving attacks or symptoms from a slow rate were the sympathomimetic amines. Epinephrine in aqueous solution or in oil was most helpful for the Adams-Stokes attacks, and ephedrine, 25 to 50 mg. four times daily, or Isuprel, 15 mg. linguets three or four times daily, aided in increasing the idioventricular rate.

Discussion

The causes of complete heart block in the present series are similar to those noted by Penton et al.[2] Coronary heart disease, with or without

hypertension or acute infarction, is apparently responsible for about 70% of instances seen in a general hospital or private practice. Slightly under half of these patients developed block without either of these complications. Among this group with only angina pectoris or healed myocardial infarction, we found a slightly higher age of onset (67.1) and a somewhat longer mean survival (48 months) than did Penton. This period of survival is about half that found in patients developing angina for the first time at the same age. There were twice as many men as women. Among the women there was a higher incidence of hypertension and diabetes mellitus.

Women with acute myocardial infarction survived longer than did men (24 months as against eight months), despite their being two years older at the time of onset and their having a higher incidence of diabetes mellitus. This is due chiefly to the high early mortality in men (50% in two weeks). The numbers surviving a month or more after the infarction are too small to permit a conclusion about prognosis.

Among patients with rheumatic heart disease no specific valvular lesion predominated. Many of them were in the age group at which symptoms from coronary heart disease might be expected, and evidence of coronary atherosclerosis was found at autopsy in several cases. Undoubtedly some of the older patients should properly be classified under coronary heart disease. The 3-to-1 predominance of males is in contrast to a slight predominance of females found by Penton.

Although an effort was made to include as digitalis-induced block any patient in whom there was suspicion of overdosage, the cases made up only 6% of the total, in contrast to the 11% noted by Penton. Examples were found in a spectrum ranging from a normal heart to one with coronary heart disease and preëxisting first and second degree block. Most of the patients were elderly, and six of the 17 died. Among the survivors the block almost invariably cleared completely. In several patients it developed with small additional doses of digitalis or during a diuresis.

The benign nature of congenital heart block was illustrated by the 17 patients in this series. Only one patient had genuine Adams-Stokes attacks, and four others had a single brief episode of syncope during fever or exercise. With few exceptions they are leading normal lives without restriction of activity. The oldest is now 65, and one patient with probable congenital heart block died at 79. Males and females were equally represented, and half of them had ventricular sepal defects with no functional impairment of the heart.

A high incidence of diphtheria has been reported among patients with complete heart block. Penton et al. found that 16% of their patients had a history of diphtheria in childhood, with a higher incidence among those with block of unknown cause. In the present series 6% gave a history of diphtheria (17 patients, in two of whom the block dated from the time of the infection). The distribution was as follows: coronary heart disease,

five; hypertension, four; rheumatic heart disease, two; miscellaneous (diphtheria), two; acute infarction, one; congenital, one; unknown, two.*

The apparent lack of deleterious influence of the Adams-Stokes syndrome on the prognosis of patients with heart block was interesting and surprising. Actually patients with these attacks survived more than twice as long from onset as those without.

Summary

Among 278 patients with complete heart block seen between 1925 and 1955, coronary heart disease, with or without hypertension or acute infarction, was the cause of the disorder in 70%. In the remainder rheumatic heart disease, congenital heart disease, digitalis intoxication or less common types of heart disease were responsible.

The Adams-Stokes syndrome occurred in 38%, and the mean survival time of these patients actually exceeded that of patients without these attacks.

In the coronary heart disease group the mean survival time for all patients was slightly over four years from onset.

There was a history of diphtheria in 6%; in two cases the onset of block could be related directly to that illness.

In all groups except congenital heart block and digitalis-induced block, males predominated about 2-to-1. Patients with congenital heart block were distinguished by their long survival time and relative freedom from symptoms.

Summario in Interlingua

In le curso de 31 annos, 350 patientes con complete bloco cardiac—documentate per electrocardiographia—esseva vidite al Hospital General de Massachusetts. Un analyse del 278 casos pro le quales le information in le dossiers es complete monstra que morbo cardiac coronari—con o sin hypertension—o acute infarcimento myocardial esseva le causa del bloco in 70%. In le remanente casos, rheumatic morbo cardiac, congenite morbo cardiac, e intoxication per digitalis esseva le causas principal.

Symptomas del syndrome de Adams-Stokes occurreva in 38% del casos, principalmente in patientes con morbo cardiac coronari. Per contrasto con isto, patientes con congenite morbo cardiac, con intoxication per digitalis, o con acute infarcimento myocardial habeva infrequentemente syncope o convulsiones. Le tempore del superviventia del septe patientes qui exhibiva le syndrome de Adams-Stokes in un del phases de lor curso clinic excedeva illo del altere patientes.

In le gruppo con morbo cardiac coronari, le superviventia medie esseva levemente plus que quatro annos a partir del declaration del bloco.

Esseva constatate un historia de diphtheria in 6% del patientes, sed le declaration del bloco poteva esser relationate directemente con ille morbo in solmente duo casos. In le resto del patientes con un historia de diphtheria, il existeva un altere adequate explication pro le complete bloco cardiac.

* Although the frequency of a positive history for diphtheria undoubtedly varies with the intensity with which it is sought, these data do not suggest that diphtheria is a cause of heart block in more than a few cases.

In omne gruppos, excepte illo a congenite bloco cardiac e illo a bloco causate per digitalis, le masculos predominava in un proportion de circa duo a un. Le patientes con congenite bloco cardiac se distingueva per lor longe superviventia e per lor relative libertate de symptomas.

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I^{131}-INDUCED HYPOTHYROIDISM IN INTRACTABLE ANGINA PECTORIS *

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INTRODUCTION

THE beneficial effect of thyroidectomy for intractable angina pectoris was first reported in 1933 by Blumgart.[1] Subsequent reports [2, 3] confirmed and extended the original observations. The hazard of major surgery in the seriously ill cardiac patient limited the number in whom hypothyroidism could be induced surgically. The introduction of radioiodine provided a simple, safe method for induction of hypothyroidism in these poor-risk patients. Numerous reports on the successful use of I^{131} in treatment of angina pectoris have appeared since 1950.[4-10]

The purpose of this paper is to present the results of I^{131} therapy of 24 euthyroid patients with severe angina pectoris followed for an average of 24 months after treatment.

INDICATIONS FOR I^{131} TREATMENT AND CRITERIA FOR SELECTION OF PATIENTS

Selection of patients described in this study has been in accord with the general agreement that I^{131} therapy should be limited to the following:

1. Patients with severe angina.
2. Patients whose angina fails to respond to conventional medical therapy such as weight reduction, limitation of activity, vasodilators, sedation, etc.
3. Patients whose symptoms have been present long enough to indicate that clinically significant spontaneous remission is unlikely.
4. Patients whose symptoms are relatively stable or only slightly progressive, but who are partially disabled.
5. Patients who are expected to live long enough to develop hypothyroidism.

The last criterion excludes patients with rapidly progressive coronary disease, recent severe myocardial infarction, malignant hypertension or other systemic disease with a limited prognosis. Hypercholesterolemia has been offered as a contraindication for I^{131} therapy. As it is not yet established

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that an increase in serum cholesterol following induced hypothyroidism significantly shortens life in these patients by accelerating chronic coronary atherosclerosis, we do not believe hypercholesterolemia is a contraindication to palliative treatment.

Consideration should be given to the patient's occupation, since retardation of mental processes following hypothyroidism may be a contraindication in specific cases.

TABLE 1

Summary of Clinical Material

Case No.	Hospital No.	Age	Sex	Duration Angina (Mo.)	Severity Angina*	Hypertension	Cardiac Decompensation	Cardiac Enlargement by X-Ray	History Myocard. Infarct.	Electrocardiographic Findings		
										(†)	(‡)	(§)
1	57973	60	M	36	1–5/d	+	−	0	−	±	+	−
2	189477	54	M	12	8–10/d	+	−	0	+	±	+	−
3	123381	42	M	8	F.C. IV	−	−		+	−	±	−
4	17729	52	F	1	F.C. III	−	−	0	−	−	−	−
5	190150	41	M	24	10–15/d	−	−	0	−	+	±	±
6	180791	45	M	13	10–20/d	+	−	0	−	+	−	+
7	271029	66	M	54	F.C. IV	+	−	0	+	+	±	−
8	299720	58	F	60	40/d	+	+	+	+	−	+	±
9	294402	55	M	120	30–45/d	+	−	0	+	−	−	+
10	297313	50	M	20	F.C. IV	−	+	++	+	+	+	±
11	293001	55	M	48	7–10/d	+	+	+	+	−	+	+
12	283528	45	F	24	2–3/d	+	+	+	−	+	−	+
13	186874	60	M	96	20/d	−	−	0	−	+	−	−
14	305816	69	F	30	F.C. III	+	−	+	+	−	±	−
15	301248	70	F	36	1–2/d	+	+	+	+	−	−	+
16	304656	46	M	66	2–3/d	−	−	0	−	+	−	−
17	297238	51	M	1	F.C. IV	−	−	0	+	−	+	−
18	176077	49	M	96	F.C. IV	−	−	0	−	+	−	+
19	270774	58	F	20	12/d	−	+	+	+	±	+	−
20	275098	59	M	24	8–10/d	+	−	+	+	+	±	−
21	292830	55	M	12	F.C. IV	+	−	0	+	−	±	+
22	282267	57	M	7	1/d	−	−	0	−	+	−	±
23	157706	59	M	3	F.C. III	−	−	0	+	+	−	−
24	40842	57	M	96	4–5/d	+	−	0	−	+	−	+

* Expressed as either the number of attacks per day or as functional capacity, i.e., II—angina on heavy exertion, III—angina on light exertion, IV—angina at rest.

† Evidence of coronary insufficiency.

‡ Evidence of previous infarction.

§ Evidence of left ventricular hypertrophy or strain.

CLINICAL MATERIAL AND METHODS

Clinical Material: The present series consists of 24 patients referred to University Hospitals for evaluation and treatment of severe angina pectoris. Their ages ranged from 41 to 70, the average being 54.7 years. The angina varied in duration from only one month in two patients up to 10 years in one patient prior to admission. Six of the patients had angina while at rest, while the remainder had noted multiple attacks of pain daily while on limited activity. An elevated blood pressure (over 150/90 mm. of Hg) was present in 13 of the 24 patients, and in six there was evidence of cardiac decompensa-

tion. This was correlated with the finding of cardiomegaly on chest x-ray. Fourteen patients gave a history of previous myocardial infarction, in seven of whom there was definite electrocardiographic evidence of previous infarction. These data are summarized in table 1.

The data on serum cholesterol levels and I^{131} uptakes are included in table 2.

Method of Treatment: The quantity of I^{131} calculated to induce hypothyroidism was given as a single dose. Subsequent treatment was given

TABLE 2

Summary of Therapy and Results

Case No.	I^{131}		Pre-Treatment		Post-Treatment		Hypothyroid Status	Severity Angina		Over-all Result
	No. Doses	Total mc.	Cholesterol (mg.%)	I^{131} Uptake (% at 24 hrs.)	Cholesterol (mg.%)	I^{131} Uptake (% at 24 hrs.)		Before*	After†	
1	3	32	280	14	400+	9.7	Severe	1–5/d	2/w	Excellent
2	1	25	236	24	435	—	Severe	8–10/d	2–6/d	Good
3	2	16	286	24	—	—	Mild	F.C. IV	F. C.III	Good
4	2	18	379	30	447	21	Severe	F.C. III	F. C. II	Good
5	1	24	367	25	470	7.5	Moderate	10–15/d	2/m	Excellent
6	2	36	816	37	—	21	Moderate	10–20/d	0–2/d	Excellent
7	2	26	250	31	490	20	Moderate	F.C. IV	1/m	Excellent
8	1	18	470	42	644	9	Moderate	40/d	2–15/d	Good
9	1	30	210	21	427	—	Moderate	30–45/d	0	Excellent
10	2	32	205	22	—	10	Moderate	F.C. IV	F.C. III	Good
11	3	56	302	31	258	15	Severe	7–10/d	0–1/d	Excellent
12	1	20	—	23	—	5	Euthyroid	2–3/d	Worse	POOR
13	3	106	—	14	483	13	Severe	20/d	0–10/d	Excellent
14	1	12	279	17	250	33	Mild	F.C. III	0	Good
15	1	15	271	40	398	9	Moderate	1–2/d	2–3/w	Excellent
16	1	20	320	25	370	—	Severe	2–3/d	0	Excellent
17	2	27.5	256	38	360	23	Euthyroid	F.C. IV	0–2/d	Excellent
18	2	25	322	17	458	3	Moderate	F.C. IV	F.C. III	Good
19	2	58	217	23	—	24	Mild	12/d	8/m	Excellent
20	2	29	215	18	236	9.5	Severe	8–10/d	1–3/d	Excellent
21	4	25	263	29	372	—	Euthyroid	F.C. IV	F.C. III	Excellent
22	4	57	210	17	397	10	Severe	1/d	0–1/m	Excellent
23	2	30	291	21	455	13	Severe	F.C. III	F.C. II	Good
24	1	16	—	15	—	15	Mild	4–5/d	0–2/w	Excellent

* Expressed as either the number of attacks per day or as functional capacity, i.e. II—angina on heavy exertion, III—angina on light exertion, IV—angina at rest.

† Expressed as either the number of attacks per day, week or month, or as functional capacity as in *.

at three-month intervals as necessary if the desired reduction in metabolism had not been produced by the initial dose, or if there had been either persistence or recurrence of the angina and it was believed that further metabolic depression would be of benefit to the patient. Dosage of I^{131} was estimated according to the following formula:

$$\text{Dose} = \frac{\text{Estimated wt. of gland} \times \text{desired tissue concentration of } I^{131}/\text{gm.}}{\text{Thyroidal uptake of test dose}}$$

The weight of the thyroid was estimated on the basis of 25 gm. for a normal size gland. The concentration of I^{131} delivered to the thyroid was in the range of 200 to 300 microcuries per gram. The concentration of I^{131} necessary to induce hypothyroidism has been from two to four times greater than the tissue concentration of I^{131} found to be necessary in the treatment of hyperthyroidism in an earlier study.[11] The thyroidal uptake of a test dose of I^{131} was determined at 24 hours by standard scintillation detector technic. Data on the dosage of I^{131} are presented in table 2.

Results

At the time of this report nine patients have been followed for less than one year after treatment, while 15 have been followed for periods of up to 52 months. The results obtained have been evaluated as quantitatively as possible, using a modification of the classification reported by Blumgart.[9] Three categories of results were used:

1. Excellent (marked improvement): This includes patients showing either disappearance of angina after treatment, or a marked decrease in frequency and severity despite increased activity; the latter was estimated as a 75 to 100% reduction in number of attacks of pain or number of nitroglycerin tablets used per week.

2. Good (worth while): Includes those with moderate decrease in frequency and severity of attacks on the same activity level, or the same frequency and severity on an increased activity schedule. The moderate decrease was estimated at approximately a 50% reduction of number of attacks or nitroglycerin tablets used.

3. Poor (not worth while): This includes those with no improvement, or less than 25% reduction in number of attacks or of nitroglycerin tablets used.

Of the 24 cases in this series (table 2), 15, or 62.5%, obtained excellent or marked improvement over their pretreatment status. Eight, or 33.3%, obtained good or worth while improvement, while only one patient showed no improvement. The patient (case 12) obtaining no improvement was followed for only three months after treatment. At the end of this time, the I^{131} uptake was reduced to hypothyroid levels (5%), although clinical hypothyroidism had not developed. A longer follow-up period to allow time for clinical hypothyroidism to develop would be necessary before concluding that improvement would not occur. These results suggest that radioiodine-induced hypothyroidism is effective therapy in selected patients with angina pectoris.

As shown in table 2, the degree of symptomatic improvement in angina generally paralleled the degree of hypothyroidism induced. Striking exceptions did occur, as several patients obtained an "excellent" result with only minimal to moderate hypothyroidism, while a few noted less favorable

results despite development of severe hypothyroidism. This is not surprising, considering the individual variation with respect to pain thresholds and the natural history of coronary artery disease. Recognition of this variability is of practical clinical importance in attempting to predict the degree of hypometabolism required to produce relief of the angina.

Four patients (cases 1, 6, 7 and 24) are dead. Autopsy was performed in one in whom coronary sclerosis, old and recent infarcts, and a mural thrombus were demonstrated. No autopsies were obtained in the remaining three patients, although the nature of their sudden deaths suggested myocardial infarction.

Discussion

The favorable results of radioiodine-induced hypothyroidism in the treatment of angina noted in this group of patients are comparable to the experience recorded in the literature. Numerous reports [4-10] indicate that from 75% to 93% of patients treated in this manner have obtained benefit sufficient to make the therapy worth while.

The absence of serious side-effects is noteworthy, in our series as well as in others. Radiation thyroiditis, nausea, temporary hypermetabolism due to rapid release of thyroxine by the radiation damaged thyroid and hematologic depression have not been encountered in this group of patients.

The symptoms of hypothyroidism have been sufficiently disturbing in some patients to cause discomfort. This is due in part to the removal of the constant threat of angina, which tends to be forgotten, and in its place is substituted a new group of symptoms to occupy the patient's attention. Tolerance for these symptoms is highly variable, depending upon the individual. Carefully adjusted therapy with desiccated thyroid in doses of 8 to 32 mg. daily has been required in several patients for reduction of severity of the hypothyroid symptoms. Fortunately, this has usually not been attended by a significant increase in frequency of angina. Occasionally, coronary reserve is so limited that any elevation of metabolism from myxedema levels will be attended by immediate recurrence of angina. This is well illustrated by the following case history:

Case Report

Case 11. A 55 year old white male had noted the onset four years before admission of severe substernal pain which lasted for five hours. Since that time he had experienced typical angina pectoris triggered by the usual mechanisms such as exertion, excitement, meals, and exposure to cold weather. He had also noted intermittent episodes of more severe pain of longer duration that did not respond to nitroglycerin or to rest. At the time of admission to the University Hospitals, in November, 1953, he was having on the average of seven to 10 anginal attacks daily.

On physical examination his pulse was 84, blood pressure 160/110 mm. of Hg. Systolic murmurs were audible at the base and apex of the heart. The liver was palpable 2 cm. below the costal margin, and there was minimal pitting edema pretibially. Chest films revealed left ventricular hypertrophy and slight pulmonary congestion. Electrocardiograms showed evidence of an old posterior wall infarction.

The patient received a total of three doses of radioactive iodine, the first in December, 1953, and the last in October, 1954. Improvement of the angina was noted in March, 1954, when he reported no more than one attack per day. This improvement continued so that by May, 1955, he reported having had only four attacks of angina in the previous three months. At this time he complained bitterly of marked intolerance to cold, numbness of the hands and feet, weakness, cramps in the legs, dry skin, hoarseness, constipation and puffiness of the face. Because of these symptoms of severe hypothyroidism he was started on desiccated thyroid, 16 mg. daily. This resulted in some improvement in the hypothyroid symptoms and at the same time caused an undesirable increase in the frequency and severity of his angina. Despite careful titration of the dose of desiccated thyroid, it was not possible in this patient to achieve a satisfactory compromise between unpleasant symptoms of hypothyroidism and significant increase in the amount of anginal pain.

It should be emphasized that induced hypothyroidism is palliative treatment. The atherosclerotic process in the coronary arteries continues until eventually the coronary flow becomes inadequate for a cardiac work load associated with a hypometabolic state. At this time, angina will recur despite marked reduction of metabolism. The following case illustrates this point:

Case 7. A 66 year old white male was admitted in June, 1950, with angina pectoris of five years' duration. This had been slowly progressive until 1951, when it occurred regularly while at rest. He received 16 mc. of radioiodine in May, 1952, and 10 mc. in October, 1952. By August, 1952, he reported very excellent relief, having noted only four anginal attacks in the preceding eight weeks. The following three years were equally satisfactory, with no more than one to two attacks of angina per month. In June, 1955, he experienced a recurrence of angina at least once daily, despite persistence of moderately severe hypothyroidism. By December, 1955, he was having three attacks of angina daily, and died shortly thereafter. Although this patient was eventually a victim of his disease, he nonetheless experienced very satisfactory palliation of symptoms for nearly three years.

Summary

Experience with 24 euthyroid patients treated with radioactive iodine for severe angina pectoris is reported. In properly selected patients with well stabilized disease that has not responded to conservative treatment, radioactive iodine induction of hypothyroidism has afforded excellent results in 62%, and worth while results in 33%. Dosage of I^{131} required has varied widely. Although the degree of symptomatic improvement of pain has usually paralleled the degree of hypothyroidism, exceptions have been observed in whom considerable benefit has been noted without disturbing symptoms of myxedema. No important side-effects of the therapy have been encountered. In several cases partial relief of distressing symptoms of myxedema has been possible without inducing a significant increase in angina. Occasionally coronary reserve will not permit any elevation of metabolism. Recurrence of angina after several months or years of hypothyroidism may be anticipated as the coronary disease follows its natural course. Radioiodine-induced hypothyroidism affords very effective and safe palliative therapy in selected patients with angina pectoris.

SUMMARIO IN INTERLINGUA

Es reportate le experientias del autores con 24 patientes euthyroide durante lor tractamento con iodo radioactive pro sever angina de pectore. In patientes appropriatemente selegite—in qui le morbo esseva ben establite e que non habeva respondite a formas conservatori de tractamento—le induction de hypothyroidismo per medio de iodo radioactive ha producite excellente resultatos in 62% del casos e resultatos que valeva le pena in 33% del casos. Le requirimentos de dosage de I^{131} variava extensemente. Ben que le grado del melioration symptomatic in le dolores experientiate per le patientes esseva usualmente parallel al grado del hypothyroidismo, certe casos esseva observate in que un beneficio considerabile esseva effectuate sin le adverse symptomas de myxedema. Nulle significative effectos lateral del therapia esseva incontrate. In plure casos, le alleviamento partial del adverse symptomas de myxedema esseva possibile sin inducer un augmento significative in le angina. In casos sporadic, le reserva coronari es tal que nulle elevation del metabolismo es possible. Le recurrentia del angina post menses e annos de hypothyroidismo debe esser expectate como evento natural in le curso morbo coronari. Hypothyroidismo inducite per iodo radioactive constitue un efficace e non-riscose therapia palliative in selegite patientes con angina de pectore.

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RHEUMATIC HEART DISEASE IN PREGNANCY: THE REMOTE PROGNOSIS IN PATIENTS WITH "FUNCTIONALLY SEVERE" DISEASE *

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IN this paper we shall review our experience with rheumatic heart disease in pregnancy and present a new analysis of the remote mortality in women having severe cardiac impairment when pregnant.

The women with rheumatic heart disease in pregnancy seen at the Margaret Hague Maternity Hospital will be presented in several separate series:

1. All such patients seen in the years 1933 to 1939. This series will be used only for the derivation of the rules for management.

2. Only the patients seen in the Cardiac Clinic from January 1, 1939, to August, 1942, and from March, 1946, to date. (The four-year hiatus represents the time that the senior author spent in military service; pertinent records are not available for this period.) This series will be used to show what can be done in the management of the pregnant women with heart disease, under the rules to be outlined.

3. All patients classified as having severe cardiac impairment, seen from the opening of the hospital in 1931 through 1943. This series will be used for the analysis of the late prognosis. All tables and graphs in this paper pertain only to this last series.

Heart disease and pregnancy have long been considered to be a bad combination. Undeniably, pregnancy imposes an augmented demand upon the heart, and experience has proved that the woman with cardiac impairment runs an increased risk of death in pregnancy. Many clinicians believe that this increased risk does not end with the delivery and puerperium, but that pregnancy may lower permanently the already compromised cardiac reserve. In addition, it seems reasonable to suppose that rearing the child may overtax the mother's capacity for effort.

As for the immediate prognosis, heart disease has become the leading cause of maternal death in a number of obstetric services in the northeastern United States and in London. This is because of the reduction in mortality from sepsis, toxemia and hemorrhage. As often happens, we have a di-

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chotomy between what is done and what can be done. The recently reported experience of several clinics indicates that nearly all cardiac deaths in pregnant women are preventable.

Fitzgerald et al.,[1] at the Cook County Hospital, lost only three of 460 Cardiac Clinic patients, a maternal mortality of 0.65%. Their simultaneous mortality in nonclinic patients with heart disease was 9.4%. MacRae [2] reports no maternal deaths in 228 cases of heart disease seen in the Queen Charlotte's Hospital. Drury et al.,[3] of the Dublin National Maternity Hospital, had no maternal deaths in 220 "booked" cases of heart disease, but a 20% mortality in their 30 emergency admissions. Ullery,[4] of the Philadelphia Lying-In Hospital, reports but a single death in 156 women with heart disease, this one death occurring in a nonregistered patient first seen on her emergency admission in cardiac failure.

These reports cover more than 1,000 pregnant women with heart disease who had had prenatal care. There were only three deaths, all in the Cook County series, and each of these followed therapeutic abortion. It is important to note that none of these was in failure at the time of surgery. The data from Dublin are of particular interest, for in this series there were no attempts at birth control, no therapeutic abortions and no sterilizations. These women reproduced almost at peak capacity. The tables show an exceptionally high proportion of older women (40% aged more than 35 years; such women are generally recognized as bad risks), and a startling incidence of severe functional impairment (38% in Classes III and IV, and 6% with auricular fibrillation). Yet not one patient died in the 220 "booked" pregnancies. It would seem that good prenatal care can offset, in a large measure, if not entirely, the extra risk that the women with heart disease assume in undertaking pregnancy.

While it is a widely accepted clinical opinion that pregnancy affects adversely the remote prognosis in heart disease, almost no one who has studied the question has been able to draw this "logical" conclusion. Jensen,[5] in his book, reviewed the literature up to 1937. There had been five approaches to the problem:

1. Anatomic studies of the heart following pregnancy.
2. Simple follow-up studies.
3. Analyses of parity in relation to age at death.
4. Comparison of nulliparous and parous women with respect to the period of survival from the first attack of rheumatic infection.
5. Derivation of death rates in relation to pregnancy and parity.

In summing up, Jensen wrote: "It may thus be finally concluded that whatever method is used, it fails to show conclusively that pregnancy *materially* alters the course of rheumatic heart disease." Nothing published since calls for any revision of his conclusion.

Flaxman [6] compared whole-life histories of 49 women pregnant 244

times to those of 41 nulliparous cardiacs. He found no difference in the age of onset of failure or in age at death. This type of statistical analysis has been criticized. It is argued that comparing nulliparous and parous patients is unfair; the woman with severe heart disease at age 20 is less likely to marry and to undertake pregnancy than is the patient with mild heart disease at the same age. In other words, this criticism suggests that the nulliparous groups might be weighted with unfavorable cases, so unfavorable as to preclude childbearing or even marriage. To offset this criticism, Boyer and Nadas [7] made a study in which they excluded all women dying before age 40. They argued that patients sick enough with heart disease at age 20 to avoid marriage or pregnancy probably would not live to age 40. When they made this exclusion, they still found no demonstrable effect of parity upon the average age at death. They also showed that parous women do not die any younger than do men with comparable lesions of rheumatic heart disease. Cohn and Lingg [8] analyzed the clinical courses and life spans of 169 women who had borne one or more children, and compared them with the courses of 215 nulliparous women. All were followed to death in the clinics of the New York Heart Association. The analysis showed no difference in the tempos of the clinical courses, no difference in the rates of development of congestive failure and no difference in the ages at death. Gorenberg and Chesley [9] approached the problem by a follow-up study. They traced to 1951 all but three of the 310 women diagnosed at the Margaret Hague Maternity Hospital as having rheumatic heart disease in pregnancy during the five-year period from July 1, 1937, through August, 1942. Of the 310 women, three could not be found, seven had died in pregnancy, and 40 proved not to have rheumatic heart disease when examined in 1951. The remaining 260 proved cases were divided into three groups:

1. Those with no pregnancy subsequent to the one that put them into the study group.
2. Those with one later pregnancy.
3. Those with two or more later pregnancies.

Comparison of these groups showed no significant differences in remote mortalities, annual death rates, or progression of cardiac impairment in those women still alive, even though the risk of later pregnancies was included.

The Diagnosis of Heart Disease

A diagnosis of heart disease should always be made with extreme caution. Obviously, no individual should be so labeled unless the evidence is conclusive. In pregnancy we should be even more circumspect, for many features of normal pregnancy mimic cardiac disease, particularly mitral disease. First, there are suggestive symptoms. Dyspnea is common in the latter months of pregnancy. Many normal pregnant women say that they

are more comfortable when sleeping on two or three pillows—orthopnea is suggested. A trace or more of ankle edema in the evening is almost a constant finding in late pregnancy. Secondly, there are suggestive signs. A mild tachycardia is normal. Clinically, there is a distinct impression of cardiac enlargement as a result of the transverse position assumed by the heart as the diaphragm rises. There are some who believe that the heart actually does enlarge during pregnancy. Increasing the confusion is the ever-troublesome systolic murmur. Our experience has taught us that a systolic murmur may be found in every pregnant woman if she is examined often enough. With the exception of a long, harsh systolic murmur over the aortic area, systolic murmurs are disregarded in our clinic unless occurring as one of a group of findings indicative of organic heart disease. Finally, the x-ray may complete the masquerade. A healthy heart may display the mitral configuration during pregnancy, and we have seen the barium-filled esophagus displaced backward by the left auricle in the right anterior oblique projection, only to have the normal contour return in the postpartum period. Again, the high level of the diaphragm in late pregnancy must be evaluated carefully and the resultant transverse position appreciated before x-ray evidence of cardiac enlargement is accepted as real. For the same reason, increased haziness of the lung bases may appear, and too often this has led to a "retrograde" diagnosis of cardiac abnormality. This combination of signs, symptoms and x-ray findings can prove most deceptive, and there should therefore be a great deal of hesitancy in diagnosing rheumatic heart disease unless the auscultatory signs are definite and conclusive.

Although all interested in this subject have expressed the need for great care in making the diagnosis of rheumatic heart disease during pregnancy, apparently the criteria used in different clinics vary greatly. In Hamilton's series [10] about 6% of the cases had mitral insufficiency diagnosed as the only valvular lesion; in our patients it is just under 4%. However, Bunim [11] recorded mitral insufficiency as the sole valvular lesion in 22% of his cases, and Tillman [12] has reported 15%. Moreover, some of the reported incidences of heart disease in pregnancy seem unduly high; Mendelson,[13, 14] for instance, has an incidence of 4.4%, which is four times that to be expected. (Mendelson's incidence is calculated from his 1944 and 1955 papers. In 1944 he wrote that from September 1, 1932, through 1943, the New York Lying-In Hospital had had 1,089 cases of rheumatic heart disease in 41,459 pregnancies. In his 1955 paper he wrote that from September 1, 1932, through 1953, they had had 2,718 cases in 78,527 pregnancies. Therefore, from January 1, 1944, through 1953, they must have diagnosed 1,629 cases of rheumatic heart disease in 37,068 pregnancies, an incidence of 4.4%. That is, one patient in every 23 was diagnosed as having rheumatic heart disease. Moreover, in the latter paper he remarked that nearly 75% of his cases had mitral stenosis. What valvular lesion did the remaining 25%

have? Aortic valvular lesions in the absence of mitral stenosis are unusual in women of the childbearing age [2.2% in our series].).

Obviously, in the face of such gross diagnostic variations in different series, over-all results cannot be compared. Possibly those who report a high incidence of heart disease and a high incidence of mitral insufficiency as the only lesion are including patients who should be classified as having "potential" or "possible" heart disease, or as patients who have no definitely proved cardiac impairment. In nearly 150,000 deliveries in our hospital there has not been a single case of heart failure in a patient with mitral insufficiency alone. Gordon [15] has analyzed all maternal deaths of women with heart disease occurring in Brooklyn in the past 15 years. Every such woman with rheumatic heart disease had mitral stenosis; not one had mitral insufficiency as the sole valvular lesion. Obviously, statistical analysis of series with high proportions of pure mitral insufficiency cannot be compared with more strictly selected groups. The former are diluted with cases who are in no danger of failure and who, at least in the opinion of some cardiologists, have no organic heart disease.

Also pertinent to this problem of diagnosis is the report of Haig and Gilchrist,[16] who followed 352 women to dates varying from one to 10 years after their last attendance at the Cardiac Antenatal Clinic of the Royal Maternity Hospital of Edinburgh. They found that 10.5% of the patients diagnosed by cardiologists as having rheumatic heart disease in pregnancy had no detectable organic lesion at follow-up. "One woman in ten, when re-examined some years after the pregnancy in which their hearts had been suspect, had in fact no organic heart lesion." Fifty per cent of these cases had been falsely diagnosed because of the presence of a mitral systolic murmur. In our own [9] follow-up study we found a 13% error. Considering the organizational differences in these two widely separated clinics, we believe this close agreement lends a ring of truth and points up the need for extreme care in making a diagnosis of heart disease in pregnancy.

Once the diagnosis of rheumatic heart disease has been made in the pregnant woman, what is the prognosis? The physiologic demand placed upon the heart by pregnancy is well documented by Hamilton and his coworkers.[10] The cardiac load begins to increase by the end of the first trimester and progresses steadily until about the seventh month. Thereafter it decreases, with a consequent diminution in cardiac work. This extra load is sufficient to embarrass a previously damaged heart unless other factors known to strain the cardiac capacity are appreciated and minimized.

Rules for the Management of the Pregnant Cardiac Patient

In a search for factors of prognostic value in the management of the pregnant cardiac, Gorenberg and McGeary [17] analyzed the 345 pregnancies in rheumatic cardiacs seen at the Margaret Hague Maternity Hospital between 1933 and 1939. In this group we had 77 cases of heart failure, an

incidence of 22.3%. This high incidence led us to formulate Rule I: Extra bed-rest. All cardiacs in our clinic are urged to spend one to two hours in bed every afternoon, and to get as much more than eight hours as possible in bed every night. Remembering the progressive rise in cardiac work in the later months, we added other restrictions of exertion in the sixth, seventh and eighth months.

In this review we were impressed immediately with the effect of age upon the incidence of heart failure. We divided our series into five-year age groups ranging from under 20 to over 40 years. We found a steady increase in the incidence of cardiac decompensation as we went up the scale in years. In general, it may be said that the older the cardiac patient, the greater the possibility of a breakdown in the pregnant state. To make the association between age and the incidence of decompensation more striking, the patients were divided into two groups: those less than 25 and those more than 25 years of age. The failure rate in the younger group was 10.2%, as compared to 33.7% in the older patients. From this finding came Rule II: The cardiac who is more than 25 years of age is observed at weekly intervals.

The relationship between the incidence of cardiac failure during the pregnancy and the functional capacity in the prepregnant state was determined. It is necessary here to interpolate that we use the American Heart Association classification, as follows:

Class I: Patients with cardiac disease and no limitation of physical activity.
Class II: Patients with cardiac disease and slight limitation of physical activity.
Class III: Patients with cardiac disease and marked limitation of physical activity.
Class IV: Patients with cardiac disease who are unable to carry on any physical activity without discomfort.

It is also important at this point to stress that in our determination of the functional class we have used the period preceding the pregnancy under study. So determined, our Class I cardiacs had a 2.8% incidence of heart failure during pregnancy; Class II, 7.7%; Class III, 72.8%; Class IV, of course, 100%. Thus the incidence of failure in pregnancy quite naturally increases as the functional capacity in the prepregnant state decreases. The burden of pregnancy can be borne without serious difficulty by the comparatively well functioning hearts, while the same burden will cause decompensation in the badly incapacitated group. From this came Rule III: All patients whose measure of functional capacity prior to pregnancy places them in Class III or IV are hospitalized at their first visit to the clinic, regardless of how well they may seem to be at the time. They are kept at absolute bed-rest for the remainder of the pregnancy.

Did the patient ever decompensate before? What a pathologic heart will do when forced to support a pregnancy may to some extent be foretold by its previous record. In our series there were 44 women who had suffered broken compensation previously. Of these, 33 (75%) failed again when pregnancy complicated the heart disease. In patients who had never decompensated before, the chance of cardiac failure when the burden of pregnancy was assumed was 14%. From this experience came Rule IV: All patients with a history of previous decompensation are hospitalized when first seen and kept at absolute bed-rest for the remainder of the pregnancy.

In analyzing the 77 failures occurring in this series we were forcefully impressed with the warnings, the danger signals that the patients gave weeks in advance of serious trouble but that went unheeded time and time again. Too often was a cough disregarded, or else looked upon as a symptom of an upper respiratory infection. Too often was leg edema passed off as normal for the stage of pregnancy. Not infrequently was a nosebleed said to result from sinusitis. Too often was increasing dyspnea noted on weekly visits and written on the chart, but its significance overlooked. And far too often did these signs and symptoms progress for weeks or even months, finally to confront the surprised observer with a frank, far advanced state of heart failure. To prevent decompensation, the slightest decrease in cardiac reserve must be searched for diligently and recognized. Symptoms and signs that may indicate a change in cardiac status should be considered as such and strict management instituted until they prove to be extracardiac in origin. From the desire to prevent this type of error came Rule V: At the first sign of any decrease in cardiac reserve the patient is hospitalized and placed at absolute bed-rest for the remainder of her pregnancy. In the clinic we tritely say that we do not see colds, bronchitis, sinusitis, etc. in our cardiacs. These patients are hospitalized as showing evidence of decompensation. The basic assumption is that nothing can happen to a pregnant cardiac except heart failure. However, if observation at bed-rest and certain tests (vital capacity, venous pressure, circulation times) indicate that this is in error, the patient is returned to an outpatient status.

The group of 345 cases afforded us an opportunity to assess the relative value of cesarean section as compared to vaginal delivery. We know of no satisfactory quantitative estimation of the amount of work done during labor and the possible resultant strain upon the heart. We know of no good way to estimate the burden placed upon the heart by cesarean section and the postoperative period. However, although we realize the inadequacy of our method, we made an attempt to judge the effects of a normal spontaneous delivery as against the effects of a cesarean section, by comparing the convalescent periods. The postpartum period in women who have had a cesarean section is accompanied by elevated temperature and pulse readings

much more often than in patients who have had a vaginal delivery. Fever was present for more than five days in 21% of the cesarean section group, as compared to 2.6% in the vaginal delivery patients. The pulse rate was over 90 for more than five days in 75% of the cesarean section patients, as compared to 19.4% in the vaginal delivery group. The possibility of vomiting, abdominal distention and pain, with their concomitant strain upon the heart, must also be appraised carefully in judging the burden to a patient of a cesarean section. And finally, the mortality rates in the two groups are of interest: of those delivered by abdominal operation, 13.8% died; of those delivered vaginally, 1.9% died. The odds are better than six to one for delivery *per vaginam*. It cannot be argued that this difference is due to a selection of the more serious grades of heart disease for cesarean section. As a matter of fact, the analysis showed the opposite to be true. The most serious cardiac patients, the Class IV cases, were all delivered by the vaginal route. It should be stressed that they were considered as too serious cardiac risks to be offered the "benefits" of cesarean section. From this experience, an increased morbidity and mortality rate following cesarean section, with the added fact that the onset of cardiac failure during labor is a rarity, came Rule VI: Surgical intervention is contraindicated. Labor is allowed to occur spontaneously, and cesarean section done only when obstetric indications exist. (In the most recent analysis done at the hospital, the incidence of cesarean section in clinic cardiacs was 1.3%, almost 99% being delivered vaginally, while the over-all hospital rate for cesarean section is about 4%).

Immediate Prognosis

Since 1939 our Cardiac Clinic has been conducted on the foregoing basic principles. From 1939 to 1942 a second group of 157 consecutive cases were managed through the Cardiac Clinic. In this group our [18] failure rate was 2.5%, as compared to the 22.3% in the original series. The death rate was 0.64% (one case), as compared to 3.47% in the original series. Several of the decompensations and the single death occurred in the first year of our experience, when the rules were not so strictly defined as now. We believe that the single death was preventable, and would not occur today. From 1946 to date we have observed over 550 additional pregnancies in consecutive Cardiac Clinic patients with rheumatic heart disease, and we are able to report a single failure and a single death. Thus, with a four-year hiatus while the senior author was in military service, and during which time the rules were not strictly applied, we now have a series of more than 700 consecutive Cardiac Clinic patients managed by him, with a total of two deaths. We wish to stress that this total includes every pregnant woman with rheumatic heart disease who registered in the Cardiac Clinic prior to delivery or prior to cardiac failure. It does not include private patients, in whom the death rate is close to 10% (of the recognized

cases), or nonregistered emergency admissions in whom the mortality approaches 20%. As Fitzgerald et al. and Drury et al. also found, the tremendous difference in mortality as between Cardiac Clinic patients and others points up the necessity for close observation and rigid adherence to the rules for management. Pregnancy is potentially lethal for the woman with definite cardiac impairment, as shown by the mortality rates in private and nonregistered patients. Pregnancy can be borne successfully by such women, as proved by the Cardiac Clinic results in our hospital, in the Cook County Hospital, in the Dublin National Maternity Hospital, and in some other institutions. Our argument is that such deaths can be prevented, not that deaths do not occur.

As in the Dublin series, no therapeutic abortions were performed in our series. In the 1,000 cases cited from the recent literature, the only maternal deaths followed therapeutic abortion (except for Ullery's one emergency admission of a nonregistered patient). It would seem that if a patient is seen early enough in pregnancy to be aborted, she has been seen early enough to be given good medical care and thus be permitted to complete her pregnancy successfully.

The risk of death in any given year is greater for a woman with rheumatic heart disease, pregnant or not, than it is for a woman with a healthy heart. Obviously we cannot be expected to reduce the maternal mortality for cardiac patients to the very low level prevailing for normal women. We cannot fairly make such a comparison, but we can compare the risk of death for the pregnant cardiac to that for the nonpregnant cardiac. Seven hundred pregnancies represent about 525 patient-years' exposure to the risk of death; two deaths in this series give an annual death rate of less than four per thousand. The annual death rate for rheumatic cardiac women generally, in the childbearing age, is about 25 per thousand, which is more than six times that for our pregnant Cardiac Clinic patients. In other words, it would seem that pregnancy had reduced the risk of death. This, of course, is fallacious. There is some natural selection of the more favorable cases in the pregnant group. Also, pregnancy brings these women under the care of a cardiologist during the period of gestation, and those with serious functional impairment are kept in bed for long periods.

Up to this point we have been concerned with the immediate prognosis for the woman who complicates her rheumatic heart disease by becoming pregnant. We have attempted to show that, with certain rigid standards of management, the immediate prognosis is excellent. The great majority of deaths in pregnant cardiac women result from decompensation; therefore, it is axiomatic that to decrease the mortality rate one must strive to decrease the failure rate. Meticulous care does reduce the failure rate and has reduced the mortality rate. By anticipating heart failure, we can prevent it. With meticulous care, with early and adequate treatment when indicated, the burden of pregnancy can be borne even by women with severe grades

of cardiac damage. In short, the burden of pregnancy itself is not be feared.

Remote Prognosis

Now, what is the remote prognosis? Does pregnancy shorten the life expectancy even though the patient survives pregnancy and delivery? While a number of investigators have concluded that pregnancy does not affect the remote prognosis, the question poses formidable difficulties. In our [9] published follow-up study of 260 women with proved rheumatic heart disease, only 34 had cardiac impairment severe enough to warrant a functional grading of Class III or IV prior to pregnancy. Realizing that our over-all results could be criticized as being weighted with patients having relatively mild heart disease, we have since studied a series of severe cardiacs delivered at our hospital and reëxamined in 1952. The remainder of this report pertains to some of the results of an analysis of the remote prognosis for women who had "functionally severe" rheumatic heart disease. As in our previous study, we compare patients who had later pregnancies to those who did not. The pitfalls in such a comparison are:

1. Patients having later pregnancies have lived long enough to do so (that is, there is a time bias).
2. Older patients, who might have a worse prognosis, are less likely to have later pregnancies.
3. Patients having later pregnancies might have milder degrees of cardiac impairment (that is, the "No Later Pregnancy" group may be weighted with the worst cases).

We believe that the data shown in the ensuing tables effectively dispose of these possible biases.

Selection of Cases with Severe Heart Disease: We have reviewed every chart bearing the diagnosis of rheumatic heart disease, covering the period from the opening of the Margaret Hague Maternity Hospital in October, 1931, through 1943. Any (and every) patient who satisfied any of the following criteria was accepted as having severe heart disease:

1. History of cardiac failure, excluding failure during an acute phase of rheumatic carditis (46 cases; eight by this criterion alone).
2. Class III or IV at the time of conception (57 cases; 11 by this criterion alone).
3. Auricular fibrillation (15 cases; only one by this criterion alone).
4. Cardiac failure in pregnancy (104 cases; 55 by this criterion alone).

The class prior to pregnancy was decided solely upon the basis of the notes in the charts. If no notation was made as to the patient's functional capacity before pregnancy, she arbitrarily was put in Class I, unless this was patently absurd; in such cases the Class was recorded as "unknown."

The effect has been to downgrade the severity of heart disease, especially in the cases seen in the early days of the hospital, when charting often was inadequate.

By these criteria we found 137 patients with severe heart disease who were discharged from the hospital. Seventy-five satisfied one criterion, 33 satisfied two, 19 satisfied three, and six satisfied all four criteria; four were dropped from the study (see below). These severe cases constituted 18% of all rheumatic cardiacs. Omitting the Class I patients who failed during pregnancy, this series represents 14% of all rheumatic cardiacs seen during the base period of 12.2 years. This proportion of severe cardiacs (14%) is very close to the 12% reported by Hamilton as "unfavorable" cases seen at the Boston Lying-in Hospital, suggesting that our series is not abnormally seeded. All but one of the 137 patients have been traced to 1952, and all but one of the survivors have been reëxamined. We have studied the charts in many hospitals of those patients who have been hospitalized, and have obtained information from several physicians who have attended these patients. The average length of follow-up is almost exactly 10 years, and ranges up to 21 years; all patients still living have been followed for at least eight and one-half years. Three of the patients, diagnosed as having rheumatic heart disease with decompensation in pregnancy, were found to have no clinical or x-ray evidence of organic heart disease at follow-up. These three, and the one untraced patient (making up the four dropped from the study), are excluded from all the analyses and tables. Thus we are left with 133 patients for study.

Method of Analysis: Many of the data to be presented are in the form of average annual death rates. These death rates are based upon patient-years exposure to the risk of death. A patient-year represents one patient followed for one year. Five patient-years, for instance, might represent one patient followed for five years, or five patients each followed for one year, or two patients followed for two and three years, respectively, or any other combination adding up to five. The last year in which a patient was observed is counted as one-half patient-year; that is, if a patient was reexamined six years and eight months after delivery, she is credited with six and one-half years of survival. The year in which a patient died is counted as a full patient-year. Thus, if she died at six years and eight months after delivery she is credited with seven full patient-years. Annual death rates, per 1,000, were calculated by dividing the number of deaths by the total patient-years and multiplying by 1,000.

While the raw data for annual death rates are interesting and valuable in their own right, we shall try to use them to ascertain whether pregnancy has an adverse effect upon the remote prognosis. The ideal set of statistics to prove this point would be a comparison of matched groups of aborted or nulliparous cardiacs and nonaborted cardiacs. We have no group of aborted or nulliparous women matched to our parous patients, but a number

(38) of our "severe" cardiacs have assumed the risk of subsequent pregnancies. If pregnancy exerts an adverse effect upon the remote prognosis, statistical analysis should show an increased annual death rate in these women. Thus, as an "internal control," we have compared two groups of women: (1) those with later pregnancies, and (2) those who had no later pregnancy after the one that qualified them for admission to this "severe" series. In the following discussion "initial pregnancy" will refer to the first pregnancy in which severe heart disease was diagnosed in our hospital; it does not refer to parity. Fifty-four of the patients were primigravidas when the diagnosis was made, but the "initial" pregnancy in the other 79 was the second, third or later pregnancy, up to the fifteenth.

TABLE 1

Remote Annual Death Rates in Severe Heart Disease

	Cases	Patient-Years	Deaths	Annual Death Rate per 1000	
				All Cases	Excluding Class I*
1. Totals, all patients	133	1321.0	77	58	75
2. No later pregnancy	95	898.5	58	64	84
3. Later pregnancy	38	422.5	19	45	55
4. Later pregnancy, interval from initial delivery to later conception	38	111.5	0	0	0
5. "Corrected" no later pregnancy (2 plus 4)	133	1010.0	58	57	74
6. "Corrected" later pregnancy, conception to follow-up (3 minus 4)	38	311.0	19	61	78

* Class I Patients: 34 represented by 421.5 patient-years with 10 remote deaths. Ten pregnant again, represented by 133 patient-years with three deaths. The interval from initial deliveries to later conceptions was 27.5 patient-years.

Direct comparison of the crude annual death rates for these two groups would be misleading because of the time bias mentioned above. Also, in assessing the possible effect of later pregnancies, we cannot credit the Later-Pregnancy group with the patient-years of survival accumulated prior to the later conceptions. Perhaps the best way to circumvent the difficulty is the one we [19] used in a similar study of pregnancy and hypertensive disease. This is illustrated in table 1, from which we shall draw no conclusions as yet. Lines 2 and 3 show the raw data, with no statistical adjustments whatever. The reckoning of patient-years (survival) begins from the time of delivery of the initial pregnancy with severe heart disease. The remote annual death rates in lines 2 and 3 show the average rates at which the two groups of patients died. Line 4 shows the accumulated patient-years for the intervals from initial deliveries to subsequent conceptions. In line 6 these patient-years are subtracted from those for the Later-Pregnancy group shown in line 3, to obtain a base for the "corrected" annual death rate in

these women. Note that the risk of death in the later pregnancies themselves enters into the derivation of the death rate.

If any of the patients who had later pregnancies had died before those conceptions, their deaths would have been charged against the No-Later-Pregnancy group. Therefore, the interval years (line 4) when their lives were at risk should be credited to the No-Later-Pregnancy group. This is done in line 5. The effect of these adjustments is to increase the average annual death rate for the Later-Pregnancy group and to decrease it for the No-Later-Pregnancy cases. Inasmuch as the two groups appear to be comparable, as will be shown, this adjustment constitutes a severe bias against the Later-Pregnancy group. Statistically, it deprives these women with marked cardiac impairment and limited life expectancy of an average of three years' survival (38 patients pregnant again; 111.5 accumulated patient-years from initial deliveries to subsequent conceptions). Another factor stacking the cards against the Later-Pregnancy group is that by the time they are entered as later-pregnancy cases they may have had severe functional cardiac impairment for longer than did the No-Later-Pregnancy cases who were entered with the initial delivery. Except for the cases accepted on the sole criterion of decompensation in pregnancy, we do not know the duration of what we have defined as "severe" impairment, in most cases. If the durations were fairly evenly balanced, as between the two groups, then the Later-Pregnancy group would average an extra three years in this stage before they were entered as later-pregnancy cases.

TABLE 2

Each Functional Class Is Proportionately Represented in the "Later Pregnancy" Group

	Class Prior to Pregnancy			
	I	II	III and IV	Unknown
All cases (133), per cent	25.6	24.0	42.8	7.6
Patients with later pregnancies (38), per cent	26.3	28.9	39.5	5.3

Matching of the Two Groups: Our method of "internal control," described above, could be subject to the same criticism as that leveled against the studies of age at death. It might be argued that only the milder cardiacs go on to have more children, even in a series of "severe" cases. Thus the question rises as to the distribution of these later pregnancies. Did they occur predominantly among the patients with less severe cardiac impairment? Table 2 partially answers this question in the negative. The 34 Class I patients included in our series—32 by reason of having failed in pregnancy, and two by reason of a prior failure (with auricular fibrillation present in one of the latter)—constitute 25.6% of the whole series. They

contributed 26.3% of the women pregnant again, and 25.5% of the later pregnancies. The 32 women recorded as having been in Class II * prior to pregnancy—25 of these admitted to this series by reason of having failed in pregnancy, and seven by virtue of a history of prior cardiac decompensation—constitute 24% of the whole series and contributed 28.9% of the group pregnant again and 27.7% of the later pregnancies. The 57 patients recorded as having been in Classes III and IV at the time of conception were admitted to the series by reason of this fact alone. (Twenty-nine of these gave a history of prior failure, and 38 decompensated in pregnancy; 21 patients fell in both groups.) They constitute 42.8% of the whole series and contributed 39.5% of the patients pregnant again and 39.2% of the later

TABLE 3

Patients with Heart Disease of Especial Severity Are Proportionately Represented in the "Later Pregnancy" Group

	Mitral Stenosis Plus Aortic Lesion	3 or All 4 Criteria for Severity	First Trimester Decompensation	Auricular Fibrillation	Class III or IV at Conception Plus History of Decompensation
All cases (133), per cent	12.8	18.8	12.0	11.3	21.8
Patients with later pregnancies (38), per cent	13.2	18.4	13.2	5.3	21.1
Patient-year representation, per cent					
All cases	9.3	14.5	10.1	9.1	18.2
Later pregnancy	9.1	13.1	10.2	6.5	16.8

pregnancies. These data give one indication that our series of women with pregnancies subsequent to the one that qualified them for inclusion in this series of severe rheumatic heart disease is not loaded in any direction.

As a further control on the distribution of the later pregnancies, we have picked out five subgroups of especial severity; their severity is indicated by the high remote annual death rates shown in the ensuing tables. Moreover, most of these patients would be aborted in many clinics, if seen early enough. Each of these subgroups has been proportionately represented in the Later-Pregnancy Group, not only by patients but also by patient-years, as table 3 shows.

Twenty-two, or 16.6%, of all the patients were sterilized at the time of the initial delivery. It might be suspected that these were the very worst cases, and that sterilization therefore had weighted the No-Later-Pregnancy group with these particularly unfavorable cases. Table 4 compares the sterilized patients to others having no later pregnancies, and to those who

* We believe that the great majority of these patients placed in Class II actually should be in Class III. The reason is that the remote annual death rate for these patients was 80 per 1,000. In another follow-up study [9] of patients whose classification was known more accurately, the remote annual death rate for Class II patients was 34, while it was 71 for Class III cases. As noted above, the classification of the patients in the present series was based solely upon often meagre notes in the hospital charts.

TABLE 4

Comparison of Patients Sterilized with the Others Who Had No Later Pregnancy

	Cases	Dead, Per Cent	Mean Years of Survival*	Mean Age at Death*	Mean Age, Survivors	Annual Death Rate per 1000†
Sterilized	22	64	10.0	37.5	42.0	56
Other patients with no later pregnancy	73	61	9.4	35.6	43.8	58
Patients with later pregnancy	38	50	11.1	34.4	41.0	61

* With some patients still alive.

† "Correction" as in table 1, with the 111.5 patient-years credited to the "Sterilized" and and "Other patients with no later pregnancy" in proportion to the numbers of cases in each group.

did have later pregnancies. Again, there is no apparent difference. The reason for this is that approximately 85% of the patients delivering at the Margaret Hague Maternity Hospital are adherents of a religion that does not countenance sterilization. The sterilizations therefore have followed the patients' religious dictates and approach random distribution insofar as the relative severity of heart disease is concerned.

To sum up, there seems to have been no disproportionate weighting of the Later-Pregnancy group with the more favorable cases. Each functional Class (table 2) and each subgroup of especial severity (table 3) have been proportionately represented among the women pregnant again. The one exception is in the small subgroup with auricular fibrillation, which falls short of its quota of later pregnancies by two cases.

Another possible bias is the age factor. Are the ages of the two groups comparable? The answer is yes. The average age at entry for the No-Later-Pregnancy group was 29.2 years, while it was 30.8 years for the women who did have later pregnancies. The average annual death rates for the two groups are very similar in every age group, whether based upon

TABLE 5

The Proportionate Distribution of Patient-Years by Age Groups When They Were Lived

Age When Patient-Years Were Lived	No Later Pregnancy				Later Pregnancy*			
	Cases	Deaths	Patient-Years	Percentage Distribution	Cases	Deaths	Patient-Years	Percentage Distribution
18 to 24	30	3	67.5	6.6	8	0	19.0	6.1
25 to 29	68	10	171.5	16.9	17	6	55.0	17.6
30 to 34	76	12	256.5	25.3	21	2	79.0	25.5
35 to 39	71	16	262.5	26.4	24	6	77.5	25.0
40 to 44	47	9	165.0	16.3	16	5	51.5	16.5
45 plus	20	8	87.0	8.5	6	0	29.0	9.3
Totals	133	58	1010.0	100.0	38	19	311.0	100.0

* Entered at the time of later conception. The interval years between initial deliveries and later conceptions are credited to the no-later-pregnancy group.

the age at entry or upon the attained age at follow-up. Moreover, these annual death rates do not increase significantly with attained age because in a series selected for severity of cardiac impairment, as this one was, age is a minor factor. More important than the fact that the average ages of the two groups are similar is the fact that the ages at which the patient-years were lived are closely comparable. This is shown clearly in columns 5 and 7 in table 5.

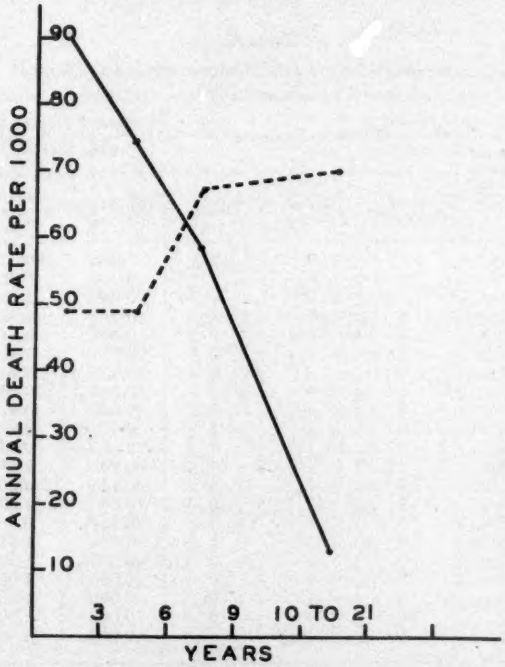

FIG. 1. Comparison of remote annual death rates, by length of follow-up, as between the no-later-pregnancy group (broken line) and the later-pregnancy cases (solid line). As in all tables and figures, the follow-up of the later-pregnancy group is begun at the time of the later conception; the years between entry into the study and the later conception are credited to the no-later-pregnancy group.

Results: The average annual death rates for the two groups of patients were shown in table 1. Even after the adjustment, which stacked the cards so heavily against the Later-Pregnancy group, there is no significant difference between the two groups. Exclusion of the Class I patients (last column) does not increase the annual death rate for the Later-Pregnancy group relative to the No-Later-Pregnancy cases, although the absolute rates are greater for both. In brief, the data shown in table 1 give no evidence that later pregnancies have increased the average annual death rate in

women with severe cardiac impairment, even though the risks of the pregnancies themselves are included in the derivation of the mortality rates.

However, there is a loophole, as is often the case when one deals with averages. The whole period of follow-up, averaging 10 years, is so long as to obscure what happened in the early years after delivery and the data of table 1 need further analysis for this reason. Figure 1 gives a clearer picture. When the follow-up is broken down into short periods, we find that the annual death rate in the first six years of follow-up is 82 per 1,000

TABLE 6

Life Table for Patients in the No-Later-Pregnancy Group*

Years After Delivery	No. in Study at Beginning of the Year	Withdrawn because of			Estimated Proportion of Survivors to Beginning of the Year Who		Cumulative Percentage Survival
		Later Conception	End of Follow-up	Deaths	Die During the Year	Survive During the Year	
1	133	3	0	9	0.068	0.932	93.2
2	121	13	0	4	0.035	0.965	90.0
3	104	8	0	4	0.040	0.960	86.4
4	92	5	0	1	0.011	0.989	85.4
5	86	4	0	7	0.083	0.917	78.2
6	75	2	0	4	0.054	0.946	74.0
7	69	0	0	4	0.058	0.942	69.7
8	65	2	0	4	0.062	0.938	65.4
9	59	0	2	5	0.086	0.914	59.7
10	52	0	1	1	0.019	0.981	58.6
11	50	0	7	4	0.086	0.914	53.5
12	39	1	1	4	0.105	0.895	47.8
13	33	0	7	4	0.136	0.864	41.3
14	22	0	3	0	0.000	1.000	41.3
15	19	0	3	2	0.114	0.886	36.6
16	14	0	5	1	0.087	0.913	33.4
17	8	0	4	0	0.000	1.000	33.4
18	4	0	1	0	0.000	1.000	33.4
19	3	0	1	0	0.000	1.000	33.4
20	2	0	1	0	0.000	1.000	33.4
21	1	0	1	0	0.000	1.000	33.4

* Patients having later pregnancies included for the periods prior to the later conception.

for the Later-Pregnancy group (adjusted as in table 1), as against 49 for the No-Later-Pregnancy cases. Five fewer deaths in the Later-Pregnancy group would be required to equalize the rates. We can account for these five deaths, for five of the women pregnant again died in one or another of the 52 later pregnancies, four in the first and one in the second later gestation. (Only one of these occurred in a Cardiac Clinic patient. It is the death recorded above in the "second group of 157 consecutive cases—managed through the Cardiac Clinic.") We have reviewed the death charts of these five patients, in different hospitals, and we believe that all deaths, including our own, were preventable. In no case were the rules for management strictly applied. (The case reports appear below.)

As might be expected, figure 1 shows that the annual death rate for the No-Later-Pregnancy group increases as time goes on. In contrast, the rate for the Later-Pregnancy group shows a sharp downward trend. The equality of the death rates for the two groups, based upon the whole follow-up, indicates that the five women dying in pregnancy probably would have died at some time in the whole period of our follow up study. The coincidence of five deaths in the later pregnancies and the excess of five deaths in the early years of follow-up of the Later-Pregnancy group, together

TABLE 7

Life Table for Patients in the Later Pregnancy Group*

Years After Conception	No. in Study at Beginning of the Year	Withdrawn because of		Estimated Proportion of Survivors to Beginning of the Year Who		Cumulative Percentage Survival
		End of Follow-up	Deaths	Die During the Year	Survive During the Year	
1	38	0	5	0.132	0.868	86.8
2	33	0	3	0.091	0.909	79.0
3	30	0	1	0.033	0.967	76.2
4	29	0	0	0.000	1.000	76.2
5	29	1	4	0.140	0.860	65.5
6	24	1	2	0.085	0.915	59.9
7	21	2	2	0.100	0.900	53.9
8	17	2	0	0.000	1.000	53.9
9	15	1	1	0.069	0.931	50.2
10	13	0	0	0.000	1.000	50.2
11	13	0	0	0.000	1.000	50.2
12	13	3	0	0.000	1.000	50.2
13	10	0	0	0.000	1.000	50.2
14	10	1	1	0.105	0.895	44.9
15	8	3	0	0.000	1.000	44.9
16	5	1	0	0.000	1.000	44.9
17	4	1	0	0.000	1.000	44.9
18	3	1	0	0.000	1.000	44.9
19	2	1	0	0.000	1.000	44.9
20	1	1	0	0.000	1.000	44.9

* Entered at the time of the later conception.

with the temporal downward trend in their annual death rate, strongly suggests that the women dying in pregnancy died prematurely. In assessing the remote effects of repeated pregnancy, one necessarily postulates that the patients survive the pregnancies. In the patients who did survive, there is no evidence that repeated pregnancy has had any adverse effect upon the remote death rate (table 1 and figure 1).

A more nearly complete picture of the data is given by life tables, only two of which we shall present in full. Table 6 shows many details of the study, such as the times of conception subject to the initial pregnancy, times of death, lengths of follow-up for the patients involved, and death and survival rates year by year. Table 7 complements table 6 in giving most of the same details for the women who did have later pregnancies; table 6 is for the No-Later-Pregnancy group and therefore includes the observations

on the women having later pregnancies, up to the time of the later conception. The last column in each table shows the percentage of patients surviving to any given year after their admission to the group. (This is the column that actuaries use in setting life insurance premiums.) Figure 2 compares the survivals of the women in each of the two groups. Note that the lines cross at the twelfth year; prior to this time, the patients in the No-Later-Pregnancy group have the higher survival rate. After the twelfth year the Later-Pregnancy cases have the higher survival rate. It just happens that the length of follow-up is such that the area between the curves before they cross is nearly equal to the area after they cross. This is the explanation

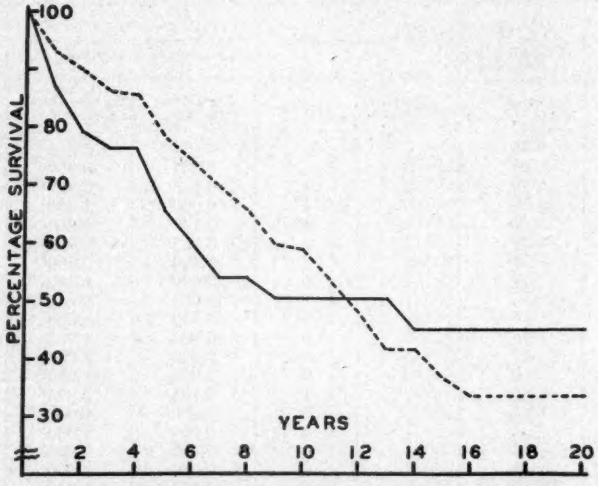

FIG. 2. Survivorship of the no-later-pregnancy group (broken line), compared to that of the later pregnancy cases (solid line).

for the equality of the average annual death rates shown in table 1. Note that the tables and figure 2 are based upon data adjusted in the manner shown in table 1 and that, statistically, the adjustment has deprived the Later-Pregnancy patients of an average of three years' survival.

Separate analyses were made for the five subgroups of especial severity, listed in table 3.

The patients with the highest remote annual death rate—106 per 1,000—were the 17 with mitral stenosis plus an aortic valvular lesion. Table 3 shows that they constituted 12.8% of the whole series and made up 13.2% of the group with later pregnancies. It is evident from table 8 that the later pregnancies have not increased the remote death rate. The annual death rates, reckoned from the time of the initial delivery, favored the Later-Pregnancy group, being 116 per 1,000 for those with no later pregnancy and 81 for those who did have later pregnancies. When we credit the No-

Later-Pregnancy group with the patient-years accumulated in the interval from initial delivery to later conception, and subtract these years from the Later-Pregnancy group, the annual death rates come out to be almost identical, at 105 and 107, respectively. (All annual death rates shown in all tables are adjusted, as in table 1.)

TABLE 8

Remote Annual Death Rates in Women with an Aortic Valvular Lesion in Addition to Mitral Stenosis

	Cases	Patient-Years	Deaths	Annual Death Rate per 1000
Totals, all cases	17	123.0	13	106
No later pregnancy	17	95.0	10	105
Later pregnancy, conception to follow-up	5	28.0	3	107

Another subgroup, with the high annual death rate of 99 per 1,000, is made up of the 25 patients who fulfilled three or all four of the criteria for inclusion in this series. Table 3 shows that they constituted 18.8% of the whole series and made up 18.4% of the group with later pregnancies. Table 9 compares the annual death rates of the two groups—those with and those without later pregnancies. The annual death rate again favored the Later-Pregnancy group, being 113 per 1,000 for those with no later pregnancy, while it is 68 for those who did have later pregnancies. Based upon the form of adjustment shown in table 1, the annual death rates are identical, at 99 per 1,000, for the two groups.

TABLE 9

Remote Annual Death Rates in Women Fulfilling 3 or All 4 Criteria for Severe Cardiac Impairment

	Cases	Patient-Years	Deaths	Annual Death Rate per 1000
Totals, all cases	25	192.0	19	99
No later pregnancy	25	151.5	15	99
Later pregnancy, conception to follow-up	7	40.5	4	99

A particularly severe subgroup is represented by those patients whose cardiac reserve is so impaired that they decompensate in the first trimester of pregnancy, before the load upon the heart is markedly increased. The remote annual death rate in this subgroup of 18 women was 97 per 1,000. Table 3 shows that they, too, were proportionately represented among the women having later pregnancies. These cases made up 12.0% of the whole series and 13.2% of those pregnant again. Table 10 sets forth the annual death rates, which are nearly identical, at 98 and 95 per 1,000. Without the adjustment for the interval years between initial delivery and later con-

ception, the annual death rates favored again the Later-Pregnancy group, being 112 for those with no later pregnancy and 68 for those who did have later pregnancies.

Auricular fibrillation, which certainly is an unfavorable development in heart disease, was present in 15 women, or 11.3% of the whole series. This is the only subgroup not proportionately represented among the women pregnant again (table 3). The two women who did have three later pregnancies each survived for 10 years after the subsequent conception.

TABLE 10

Remote Annual Death Rates in Women Suffering Cardiac Decompensation in the First Trimester of Pregnancy

	Cases	Patient-Years	Deaths	Annual Death Rate per 1000
Totals, all cases	18	134.0	13	97
No later pregnancy	18	102.5	10	98
Later pregnancy, conception to follow-up	5	31.5	3*	95

* One patient died in a later pregnancy.

The fifth subgroup of especial severity is made up of the 29 women in Class III or IV at conception and who, in addition, had had a previous bout of failure. They constitute 21.8% of the whole series and 21.1% of the group pregnant again. Table 11 shows the remote annual death rate to be 83 per 1,000 for the entire subgroup. The death rates are 85 for the No-Later-Pregnancy group and 77 for the Later-Pregnancy cases, when the No-Later-Pregnancy group is credited with the interval years from initial

TABLE 11

Remote Annual Death Rates in Women in Class III or IV at Conception Plus a History of Cardiac Decompensation

	Cases	Patient-Years	Deaths	Annual Death Rate per 1000
Totals, all cases	29	241.0	20	83
No later pregnancy	29	189.0	16	85
Later pregnancy, conception to follow-up	8	52.0	4*	77

* One patient died in a later pregnancy.

delivery to later conception. Without this adjustment, the rates were 95 and 55, again favoring the Later-Pregnancy group.

The annual death rates shown in tables 8 through 11, for the severe subgroups, are based upon the whole period of follow-up, as were those shown in table 1. Is there a loophole in that the length of follow-up obscures the deaths in the later pregnancies? Because there are so few cases in each subgroup, all five subgroups have been pooled in table 12. This gives us 53 patients, because some patients appear in two or more of the

subgroups. Only one of these patients pregnant again died in a later pregnancy (no prenatal care). Comparison of the No-Later-Pregnancy and the Later-Pregnancy groups shows no significant difference in the mortalities. Unfortunately, we have too few cases to work with. For instance, in the second three-year period, one less death in the Later-Pregnancy group would reduce the annual death rate from 118 to 78, or the addition of only seven patient-years would drop it to 92, which was the rate for the No-Later-Pregnancy cases in this period. Insofar as the limited data go, they give no evidence that repeated pregnancy has an adverse effect upon these women with especially severe cardiac impairment. If the worst cases are not affected unfavorably, it does not seem likely that an adverse effect would be seen in women with milder heart disease.

TABLE 12

Combined 5 Groups of Especial Severity (No Duplications)
Interval years credited to No-Later-Pregnancy group

Years of Follow-up	No later pregnancy			Later pregnancy		
	Patient-Years	Deaths	Annual Death Rate per 1000	Patient-Years	Deaths	Annual Death Rate per 1000
First 3	131.5	12	92	34.0	4*	118
Second 3	87.5	8	92	25.5	3	118
Third 3	59.5	5	84	14.0	1	72
10 to 21	38.0	6	158	22.0	1	46
Totals	316.5	31	98	95.5	9	94

* One patient died in a later pregnancy.

One more factor will be considered: the parity of the patients at the time of entry into the study. Does the multipara, who has withstood the test of previous pregnancies, have a better prognosis than has the primipara? If so, our study would be biased because of the predominance of women who were multiparous when admitted to the series (79 multiparas and 54 primiparas). We shall forego the details and present only the survivorship curves. These curves are derived from the last column in life tables similar to those shown in tables 6 and 7, and are comparable to figure 2.

Figure 3 compares the No-Later-Pregnancy and Later-Pregnancy groups who entered the study as primiparas. The survivorships are very similar over the first 10 years. In the first year there is one excess death in the Later-Pregnancy group. Actually, two of these women died in the later pregnancies, at two and four years after the initial deliveries. Because the interval years between initial delivery and later conception are credited to the No-Later-Pregnancy group, they show as first-year deaths in the Later-Pregnancy group. One patient had had no prenatal care and died within 12 hours of admission to the hospital, in the twentieth week of gestation. The other was first seen in failure, in the fifteenth week of gestation. After improving somewhat, she signed a release and did not return to the clinic.

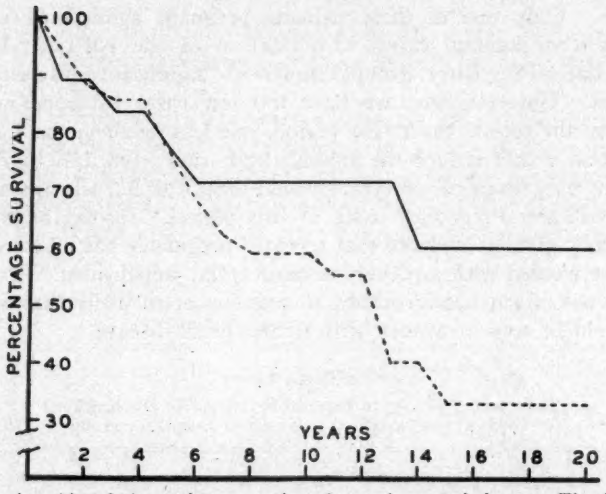

FIG. 3. Survivorship of the patients entering the study as primiparas. The broken line represents the no-later pregnancy group and the solid line the later-pregnancy group.

At 20 weeks she was re-admitted in terminal failure and died within five hours. Figure 3 seems to indicate that later pregnancies do not affect the survival of primiparous women with severe cardiac impairment, although two did die in the later pregnancies.

Figure 4 compares the survivals of the No-Later-Pregnancy and Later-Pregnancy cases who were entered as multiparas. In the first two years

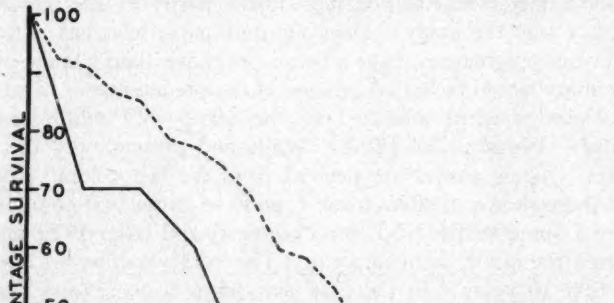

FIG. 4. Survivorship of the patients entering the study as multiparas. The broken line represents the no-later pregnancy group and the solid line the later-pregnancy group.

after the subsequent conception the women with later pregnancies die at a much faster rate than do those who do not become pregnant again. Three of the deaths occurred in the later pregnancy, to account for all of the first-year deaths. Three more occurred in the second year, within months of the subsequent delivery. Because of the few cases (20 pregnant again), the three deaths in pregnancy largely account for the wide divergence between the curves. For this reason, it would appear that pregnancy has no adverse effect, provided the patient survives the pregnancy. As we have indicated, we believe that the deaths in pregnancy were preventable. These may be summarized as follows:

Case Reports

Case 1. This 32 year old para 2–2–0–2 was the Cardiac Clinic patient mentioned before. She had decompensated in her fourth pregnancy and was in functional Class III prior to her fifth and fatal pregnancy. The patient was hospitalized in good condition when first seen in the third month of pregnancy and was kept at bed-rest for three months. Her condition seemed so good that she was allowed "bathroom privileges." (It should be stressed that this is contrary to our rule, but it happened in 1940 before we had hardened in the present mold.) Gradually she assumed more and more activity. At 32 weeks' gestation an acute pulmonary edema occurred. Premature labor and a precipitate delivery followed within 12 hours, and she died less than 20 hours after the onset of distress. It is possible that strict adherence to the rules of management might have prevented this death.

Case 2. This 44 year old woman who had decompensated in her preceding pregnancy was in congestive failure when she registered in the Clinic, in the fifth month of her fourteenth pregnancy. She had a greatly enlarged heart, mitral stenosis, aortic stenosis and auricular fibrillation. By history, she had been in functional Class III prior to conception. She developed a very severe acute toxemia of pregnancy and was delivered of a six and one-half month stillbirth after induction of labor by means of a Voorhees' bag. She died on the thirty-fourth day post partum after a prolonged septic course. She was in cardiac failure and also gave evidence of pulmonary infarction (or pneumonia). This patient was already decompensated when first seen. The superimposition of severe toxemia and severe puerperal sepsis in the days prior to the era of sulfonamide and antibiotic therapy added up to a fatality. It is conceivable that this death could have been prevented if the patient had presented herself before the onset of cardiac failure. We firmly believe that at least the decompensation could have been prevented.

Case 3. This 36 year old patient was admitted to another hospital in the twelfth week of her sixth pregnancy, in cardiac failure and with anemia. After being given a large number of different, nonspecific medications, but no digitalis or hematinic, she was sent home by ambulance three weeks after admission. She was re-admitted to the same hospital in the sixth month of pregnancy, again in cardiac failure and anemic. During this final two-week stay she was given many infusions of plasma, one 500 ml. whole blood transfusion and several 1,000 ml. infusions of Amigen, in combination with a vast array of nonspecific drugs and various dietary measures. She "suddenly died after vomiting." The treatment obviously was unorthodox and, if anything, contributed to her death. Discharging the patient after her first admission was ill-advised. Our experience has shown that if a pregnant patient is discharged after recovery from failure, she will invariably return to a decompensated state, usually more severe than the original episode.

Summary and Conclusion

A system of management of heart disease in pregnancy has been evolved. It is stressed that certain patients require absolute bed-rest during pregnancy.

We believe that the evidence presented shows unequivocally that therapeutic abortion is unnecessary and cesarean section not indicated.

Competent management reduces the inroads made upon the cardiac reserve during pregnancy to the point where decompensation and death are rarities. Practically every patient with rheumatic heart disease can be carried successfully through pregnancy. There is a dichotomy between what can be done and what often happens.

Follow-up studies are reported which seem to force the conclusion that pregnancy is a temporary complication of heart disease. There is nothing to suggest that the heart is damaged by childbearing, or that the course of the rheumatic process is thereby accelerated.

Repeated pregnancies do not increase the remote annual death rate. However, more detailed analysis shows that in the past the deaths in the later pregnancies have occurred prematurely. We believe that these deaths were preventable, for none of the patients had been managed in accordance with the rules.

The final conclusion would seem to be that if a patient with rheumatic heart disease is seen early enough in pregnancy to be aborted therapeutically, she has been seen early enough to be given good prenatal care and thus be allowed to complete a successful pregnancy which will not shorten her life.

Acknowledgments

We wish to thank the Medical Directors and Record Room personnel of a dozen hospitals, including all in Hudson County, for access to their admission files and patients' charts. Many Election Boards have coöperated fully, as have many local Boards of Health. Dr. Harry Perlberg and Mr. Don. Casciano did the x-ray work.

We are particularly grateful to Dr. John Fertig and his staff, especially Dr. Agnes Berger, for their great assistance in the statistical analysis of the follow-up data. Dr. Schuyler Kohl also helped us in this regard.

Summario in Interlingua

In un serie de plus que 700 gravidas con rheumatic morbo cardiac, surveliate per le autor senior al Maternitate Margaret Hague, solmente duo mortes ha occurrite, e ambes esseva considerate como prevenibile. Le principios del regime pro tal gravidas cardiac es (1) reposo additional, specialmente durante le sexte, le septime, e le octave mense, (2) visitas septimanal pro omne patientes de etates de 25 annos o plus, (3) reposo in lecto durante le curso del pregnantia pro omne cardiacas de Classe III e Classe IV e pro illas con un historia de discompensation, (4) hospitalisation pro le investigation del minime suspicion que le reserva cardiac ha comenciate decrescer, e (5) section cesaree exclusivemente pro rationes obstetric.

Omne dossier exhibiente le diagnose de morbo cardiac esseva examinate pro le periodo depost le inauguration del hospiral in 1931 usque al fin de 1943. Esseva segregate le dossiers de omne le casos que satisfaceva un o plures del sequente criterios: (1) Historia de insufficientia cardiac, (2) Classe III o Classe IV al tempore

del conception, (3) fibrillation atrial, e (4) insufficientia cardiac durante le pregnantia. Le serie de casos assi constituite numerava 137. Omnes, con un exception, esseva traciate usque al anno 1952. Tres del patientes habeva nulle morbo cardiac al tempore del re-examination e esseva excludite ab le studio. Le remanente 133 patientes esseva dividite in duo gruppos, i.e. patientes con e patientes sin pregnantias post illo responsabile pro lor inclusion in le serie. Esseva constatate que le duo gruppos esseva comparabile quanto a lor classification functional, quanto al severitate de lor morbo cardiac (judicate secundo cinque criterios), quanto a lor etate al tempore de lor inclusion in le studio, e quanto al etate a que illas moriva o que illas attingeva durante le periodo del observationes posterior.

In compilar le tabulas de mortalitate e in calcular le mortalitate annual, le annos de superviventia ante le subsequente conception esseva cancellate in le gruppo a pregnantias subsequente e portate al credito del gruppo sin pregnantias subsequente. Le mortalitate annual medie in le duo gruppos esseva le mesme. Isto indica que pregnantias subsequente non augmenta le mortalitate—non mesmo in consequentia del riscos inherente in le pregnantia per se. Un plus raffinate analyse del superviventia super le base del tabulas de mortalitate monstrava que cinque feminas moriva prematurmente in le curso de pregnantias subsequente. Le reportos de iste casos indica que nulle de illos esseva manipulate secundo le supra-listate principios, e iste mortes poteva esser considerate como prevenibile. Omne le analyses indicava que le pregnantias subsequente habeva nulle effecto super le curso del morbo cardiac e que le superviventia probabile non es reducite per repetite pregnantias, si le patientes supervive al pregnantias—un condition que pote esser complite per adoptar un appropriate regime.

Le conclusion es formulate que un femina con rheumatic morbo cardiac qui se presenta al medico satis tosto pro render possibile un abortion therapeutic es un femina qui se presenta al medico satis tosto pro obtener le typo de assistentia prenatal que permitte a illa completar su pregnantia a bon successo e sin risco de accurtar le duration de su vita.

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BASAL METABOLIC RATE, PROTEIN-BOUND IODINE AND RADIOACTIVE IODINE UPTAKE: A COMPARATIVE STUDY *

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THE diagnosis of typical thyroid dysfunctional states is usually not difficult when approached from either a clinical or a laboratory viewpoint. There are, however, some patients in whom hypothyroidism or hyperthyroidism is suspected, but the clinical picture is not complete or clear, and the laboratory tests are in disagreement. For these reasons, we in the laboratory have received many inquiries from various members of the Department of Internal Medicine of this hospital as to which of the three commonly used tests of thyroid function is the most reliable. We of course sought information in the literature,[2, 3] and at the same time realized that answers must be found relating to these tests—the basal metabolic rate (BMR), the protein-bound iodine (PBI), and the radioactive iodine uptake (RAI)—as performed in our own hospital facilities. We were further stimulated to conduct this study by such challenging statements from the literature as, "In its present form, the PBI determination is certainly not easily adaptable to the clinical medical laboratory of the average community," [2] and, in an editorial from the same journal, "Most clinics are not able to solve the problem of contamination and have abandoned this procedure (PBI) as a routine test of thyroid function"!

MATERIALS AND METHODS

It was agreed by all concerned that in the case of any patient referred to the hospital laboratory (BMR or PBI) or x-ray department (RAI) for any one of these tests, all three would be performed provided the referring physician agreed to complete a form containing significant data about the patient. This was to be continued until 100 patients had been so examined. The referring physician was asked to render on the abovementioned form a statement as to his clinical estimation of the patient's thyroid functional status. Charges were adjusted during this study so that all three tests were performed for the price of one. In all, we did these three test procedures on 105 patients, and of these we finished with 77 which were satisfactory for analysis in this study. On the remaining 28 either the referring

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physician did not return the form or the necessary information was not included in the answers.

The PBI was performed by the method of Zak as modified by O'Neal and Simms.[4] This is a chemical digestion method and does not involve the use of any equipment not regularly found in the average hospital laboratory. To avoid contamination and other difficulties, this test, along with several others in a similar category (e.g., 17 hydroxycorticoids), is performed in a separate small room at some distance from the rest of the laboratory, called the Special Procedures Chemistry Laboratory. Our normal values for the PBI are 4 to 8 micrograms.

The BMR is determined with a standard, commercially available machine (Sanborn). This apparatus uses a bellows rather than a water system, and uses oxygen from a tank. The test is done in the morning with the patient in a fasting and supposedly basal status. Two curves are run on each patient and the results are averaged, unless one appears to be grossly erroneous or irregular. Our normal values for the BMR are minus 10% to plus 15%.

The RAI in this hospital is performed in the x-ray department. The method uses 24-hour uptake over the thyroid gland after an oral dose of 15 microcuries. Counts over the gland are made in four different areas, and these are averaged for the final reading.

Before attempting to evaluate the clinical accuracy of a laboratory test one must have some knowledge of the precision and reproducibility of the procedure itself. We therefore performed 20 analyses on 10 specimens (each in duplicate) and calculated the PBI standard deviation, using the formula $SD = \sqrt{\frac{\Sigma d^2}{2n}}$. The result was .56 μg. The precision of the PBI was further controlled by doing daily determinations on pooled serum obtained from blood bank pilot tubes and residua from premarital serology tubes. These results were invariably between 4.5 and 7 μg.

Similarly, we calculated the standard deviation (SD) for the BMR and found it to be 6.2%. This was simple to accomplish because, as mentioned above, all BMR examinations are run in duplicate. This result was calculated from 10 patients (20 curves); because the figure was larger than we had anticipated it was again calculated from the preceding 10 patients (it is to be noted here that the technician performing the BMR did not know that we were going to calculate SD from the results), and the figure was almost identical.

Standard deviation was not calculated for the RAI.

In age, the 77 patients varied from 13 to 69 years, the great majority being between 20 and 50. There were nine males and 68 females. This is in accord with our many years of experience with the BMR alone, in that thyroid dysfunctional states are far more frequently suspected in females than in males.

In the evaluation of the results in this survey each test was considered as a unit, and the clinical impression was also given a unit value. It is to be emphasized here that the clinical impression does not represent a final clinical diagnosis, but rather the initial impression of the physician who referred the patient for these laboratory studies. Thus we had four factors to evaluate.

Results

Of the 77 patients found suitable for analysis, all four factors were in agreement in 26. Of these, four were hypothyroid, three were hyperthyroid and 19 were euthyroid. The 19 patients who were euthyroid had been referred for thyroid function studies because of a goiter.

A factor was called in error if it was in disagreement with the other three factors. The number of times each factor was so considered erroneous is as follows:

Clinical Impression—22 (28%)
BMR — 8 (10%)
RAI — 5 (6%)
PBI — 2 (2.5%)

Of the 22 patients in whom the clinical impression was erroneous by laboratory evaluation, it is interesting to note that all were euthyroid according to the three laboratory tests. The clinical impression in these 22 patients was that 13 were hypothyroid and nine were hyperthyroid.

Of the eight patients in whom the BMR stood alone in error, seven were euthyroid with the clinical diagnosis of anxiety state, and these had BMRs from plus 18 to plus 41. One patient had a curious BMR of minus 6 with a PBI of 10.6, an RAI of 74 and a clinical impression of hyperthyroidism.

There were 10 puzzling cases in which the clinical impression and the BMR were in agreement—that the patient was either hypothyroid or hyperthyroid—and the PBI and RAI were in the euthyroid range (table 1). It is to be noted here that had we considered 20% to be the lower limit of normal for the RAI, cases 38 and 78 would have added two more errors

Table 1

Case	BMR	CI	PBI	RAI	Final Diagnosis
1	+32%	Hyper	6.5	44%	Hyperthyroid
5	−11%	Hypo	8.0	28%	Euthyroid
14	+25%	Hyper	7.0	24%	Euthyroid
16	+27%	Hyper	7.75	20%	Euthyroid
23	−17%	Hypo	6.4	20%	Euthyroid
35	+26	Hyper	7.0	31%	Euthyroid
38	−17%	Hypo	6.25	17%	Hypothyroid
43	+29%	Hyper	5.4	30%	Euthyroid
78	−13%	Hypo	5.0	17%	Hypothyroid
80	+26%	Hyper	6.25	21%	Euthyroid

TABLE 2

Case	BMR	CI	PBI	RAI	Final Diagnosis
4	+30%	Hypo	8.1	13%	Euthyroid
8	−4%	Hyper	10	2%	Euthyroid
10	+32%	Hyper	11.4	6%	Euthyroid
19	+2%	Hypo	13	3%	Euthyroid

to the PBI column. We must, however, in all laboratory measurements draw lines somewhere to define normal values and at the same time realize that there are usually small, indefinite zones of "I don't know" at each end of the normal range. The final clinical diagnoses on these 10 patients are recorded in the sixth column of the table. It is worthy of note that in eight of these 10 cases the final diagnoses agreed with the results of the PBI and RAI and not with the original clinical impression and BMR.

Four other cases are of interest in that there was wide divergence between the PBI and RAI (table 2). It was found later, after further history of a really searching type, that cases 8 and 10 had been taking iodine in disguised form on the suggestion of friends. We suspect that cases 4 and 19 had also received exogenous iodine in considerable quantity, but we were unable to establish this.

DISCUSSION

We have learned by this study that even with the addition of the RAI and PBI to the BMR the diagnosis of thyroid dysfunction is difficult. The calculated error rate of 27% for the clinical impression is really excellent when one considers that the clinicians were requested to render an opinion usually after they had seen the patient but once. Actually, the relative low error rate in this series for the BMR was somewhat surprising, and I believe it offers evidence that this is still a good test of thyroid function.

The difference in accuracy between the PBI and the RAI is probably not of great significance. However, the PBI is slightly less subject to error, is considerably easier as far as the patient is concerned, and in our hospital is less costly than the RAI. It is possible that the normal ranges established for the RAI are too wide. This point is under study at present.

Our normal values for the PBI of 4 to 8 μg./100 ml. were set after doing a series of normal sera obtained from the blood bank and after a study of the literature. I believe that the ranges set by Blackburn and Power [3] and Sunderman and Sunderman [5] are too wide. The probable reason that these investigators found results that were occasionally below 4 or above 8 μg. in euthyroid persons is that their standard deviation values of 1.2 and 1, respectively, are high. Indeed, they are high enough to explain the values of under 4 or above 8 μg. in a small percentage of euthyroids on the basis of expected technical error in the test. We are at present reasonably satisfied that our values are proper for the test as performed in our laboratories.

Summary and Conclusion

We have performed three tests of thyroid function—BMR, PBI and RAI—on a series of patients referred to this hospital for any one of these three tests. Our results indicate a 10% error rate for the BMR, 6% for the RAI, and 2.5% for the PBI.

We believe that for a routine test the PBI is to be preferred because it is slightly less subject to error, easier for the patient and, in our hospital, is less expensive. However, we agree with others [2] who have stated that when difficult diagnostic problems in thyroid disease are encountered all available tests of thyroid function may be necessary for proper evaluation of the patient.

Summario in Interlingua

Pro evalutar le relative accuratessa clinic de varie tests laboratorial del function thyroide, nos ha determinate le intensitate del metabolismo de base (IMB = BMR in le texto anglese), le mesura de iodo ligate a proteina (ILP = PBI in le texto anglese), e le acceptation de iodo radioactive (AIR = RAI in le texto anglese) in un serie de patientes qui habeva essite inviate a iste laboratorio hospitalari pro le execution del un o del altere del tests mentionate. Le datos pertinente a 77 patientes esseva de character usabile in nostre analyse. Le resultatos monstrava un incidentia de valores erronee—i.e. de non-concordantia con (1) le duo altere tests e (2) le impression clinic—amontante a 10% pro IMB, 6% pro AIR, e 2,5% pro ILP.

Le accuratia technic esseva evalutate pro ILP e IMB per le methodo del deviation standard. Isto esseva 0,56 microgrammas pro ILP e 6,2% pro IMB. Iste methodo mesura le error laboratorial que inhere in le test per se.

Le conclusion esseva que le determination de ILP es le melior del tres tests pro le evalutation routinari del function thyroide. In illo le probabilitate de errores es levemente plus basse, e su execution es plus facile ab le puncto de vista del patiente e minus costose ab le puncto de vista del hospital. Nonobstante, nos nos trova de accordo con le autores qui insiste que in casos de difficile problemas diagnostic in le campo de morbo thyroide il pote devenir necessari servir se de omne disponibile tests del function thyroide pro obtener un adequate evalutation del patiente.

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THE INFLUENCE OF PENICILLIN THERAPY ON THE EMERGENCE OF KLEBSIELLAE IN SPUTUM*

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As a result of a recommendation to assign the bacteria formerly designated *Klebsiella pneumoniae* and *Aerobacter aerogenes* to a single taxonomic group to be known as Klebsiella, and to distinguish individual strains included in this new group on the basis of capsular reactivity with specific antisera,[1, 2] it seemed necessary to reëvaluate the clinical significance of these organisms when they occur in secretions of the respiratory tract. In a recent preliminary report by the authors [3] it was shown that Klebsiella could be isolated from nasopharyngeal secretions of patients without overt clinical respiratory tract disease as well as from the sputum of those with obvious disease. Also, it was shown that these organisms could be classified in two broad categories, based on the severity of the pulmonary process with which they were associated: one, comprising serotypes 1 to 4 (hereinafter referred to as "lower serotypes"), and the other comprising serotypes of higher number (hereinafter referred to as "higher serotypes"). Evidence was presented to show that the lower serotypes, classically associated primarily with the respiratory tract, are relatively uncommon in comparison with the higher types, and are more often associated with destructive lung disease, such as abscesses and atelectasis.

Among patients with lower respiratory tract disease on the medical wards of this institution, Klebsiellae have become a rather common finding in the course of routine sputum examinations; 23.2% of 99 patients have been shown to harbor these organisms at some time during the course of their hospitalization.[3] In most instances the organisms which have been isolated were found to be the higher serotypes. Occasionally these seemed to bear some etiologic relationship to the patient's disease, but often this was not obvious. Consequently, it seemed to us that a determination of the sources of origin of these bacilli might conceivably contribute to our ability to evaluate the significance of their presence in sputum.

It is well known that the use of antibiotics is frequently associated with alterations in the microbial flora resident in or upon certain parts of the body.[4-10] The changes which have been described most often consist of

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suppression or temporary elimination of those organisms susceptible to the antibiotic in use. If the indigenous flora is a mixed one, the resistant members remain unaffected and may even come to predominate. It has also been suggested that certain microörganisms may come into prominence as a result of direct stimulatory activity by antimicrobial drugs.[11, 12] Most of the time the antibiotic-resistant replacement organisms exert no demonstrable, clinically important effects, and disappear upon termination of administration of the antibiotic. Occasionally, under proper conditions, they have been incriminated as incitants of superinfections. The foregoing statements comprise a concept which implies that during a period of antibiotic administration the resistant organisms which ultimately come to predominate in a specific secretion were already present in it prior to therapy, but that their presence was masked by the antagonistic activities of the more abundant and prolific members of the microbial community. Superficially, this concept would seem to offer an explanation for the source of origin of sputum Klebsiellae (higher serotypes), especially since an earlier study [3] of the presence of these bacilli in serial sputum specimens of 43 patients examined prior to and during therapy with various antibiotics suggested that these organisms occurred more frequently after therapy than before it, particularly when the antibiotic employed was penicillin. A similar cause-and-effect relationship did not appear to exist when the isolated Klebsiellae were of the lower serotype group. The latter experience, coupled with the demonstration of Klebsiellae in the sputum of patients not receiving antimicrobial therapy, justified a reluctance to accept the "penicillin-replacement flora hypothesis" as the exclusive explanation for the source of origin of these organisms without more definite experimental evidence. The present report is concerned with the description and presentation of results of experiments carried out in an effort to determine the existence of a relationship between penicillin therapy and emergence of higher serotype Klebsiellae in sputum.

Materials and Methods

Experiment No. 1: This was carried out in an attempt to demonstrate suppression of penicillin-sensitive organisms with simultaneous unmasking of Klebsiellae under in vivo conditions. Fourteen patients with pulmonary disease of various kinds and from whose initial, prepenicillin sputum cultures Klebsiellae could not be isolated by our routine methods of examination * were treated with procaine penicillin G in a dosage of 300,000 units intramuscularly twice a day. This dosage form and schedule of administration is the one which is usually employed on the wards of this institution. Peni-

* Routine sputum examination consisted of streaking a 4 mm. loopful of sputum on plates of tryptose phosphate agar (Difco), fortified with 6% defibrinated equine blood and brom thymol blue lactose agar. Following overnight incubation at 37° C. under aerobic conditions, the plates were examined macroscopically, Gram-stained "sweep" smears were prepared and examined microscopically, and finally pure culture isolates of all recognizably dissimilar colonies were made and used for species identification. The criteria employed for the identification of Klebsiellae are those listed elsewhere.[1, 13]

cillin administration was continued for periods varying from two to six days, following which the sputum was again cultured.

Experiment No. 2: The primary objective of this test was the same as that of the preceding one, except that the conditions of its performance were somewhat different. All sputum specimens, regardless of their origin within the hospital, collected during the period September 27, 1956, to October 25, 1956, and sent to the laboratory for routine examination for pyogenic bacteria, were included. The procedure employed in their examination was the same as that described for experiment No. 1, but, in addition, included blood agar-penicillin plates, one containing penicillin in concentration of 1 unit per milliliter and the other of 5 units per milliliter. Preliminary testing had shown these concentrations to be adequate for suppression of

TABLE 1

The Composition and Alteration of Sputum Microflora Preceding and Following Intramuscular Injection of Procaine Penicillin G in 14 Patients

Organism	Number of Patients Whose Sputum Yielded Indicated Organisms	
	Preceding Penicillin	Following Penicillin
Diplococcus pneumoniae	10	10 (1)*
Streptococcus viridans	11	6 (2)
Neisseria sp.	13	2 (1)
Streptococcus pyogenes	5	3 (2)
Micrococcus pyogenes var. *aureus*	2	1

* The numerals in parentheses represent those patients in whose sputum the indicated organism was found only in the postpenicillin specimen.

penicillin-sensitive organisms, such as *Diplococcus pneumoniae, Streptococcus pyogenes* and *Streptococcus viridans,* but insufficient for inhibition of a large number of different Klebsiella serotypes. A total of 104 consecutive sputa originating from 73 patients was evaluated by this procedure.

RESULTS

With the use of the procedure described in experiment No. 1, it was not possible to demonstrate the appearance of Klebsiellae in any of the sputa of 14 patients treated with twice daily intramuscular injections of procaine penicillin G, 300,000 units per injection. The duration of penicillin therapy varied slightly: in nine patients it was three days, in two patients four days, and in each of the remaining three patients it was two, five and six days, respectively. Thus the total amount of administered penicillin varied from 1.2 to 3.6 million units, the average per patient being slightly more than 2 million units.

The composition of the aerobic microflora of the sputum of these patients before and after penicillin administration is shown in table 1. *D. pneumoniae* occurred in the prepenicillin sputa of 10 patients; nine of these continued to harbor the organism following the termination of penicillin. In an additional patient the organism occurred only in the postpenicillin specimen.

Str. viridans persisted in the sputum of four of 11 patients in whose secretions this organism was found prior to therapy. In two other patients it was demonstrated only in the post-treatment specimen. The sputum of only one of 13 patients yielded persisting Neisseria species, indicating rather effective suppression of these organisms. In an additional patient these bacteria occurred only in the postantibiotic specimen. While the frequency of its isolation from pretreatment specimens was somewhat less than that of other organisms, *Str. pyogenes* persisted in the sputum of one out of five patients. There were two instances where its isolation was accomplished

TABLE 2

Aerobic Bacterial Pathogens Isolated from Sputum Cultured on Media With and Without Penicillin

(104 Clinical Specimens Originating From 73 Patients)

Pathogen	Penicillin-free Media			Media with Penicillin	P.S.U.I.*
	Number of Sputa Showing Pathogen	Number of Patients with Pathogen	Incidence of Pathogen Per Cent (Patients)	Number of Patients with Pathogen	
(1)	(2)	(3)	(4)	(5)	(6)
Diplococcus pneumoniae	76	58	79.4	0	0
Streptococcus viridans	80	52	71.3	4	0.08
Klebsiella sp.	18†	13	17.8	15	1.15
Micrococcus pyogenes var. *aureus*	17	10	13.7	4	0.40
Pseudomonas sp.	9	7	9.6	7	1.0
Paracolobactrum sp.	7	6	8.2	5	0.83
B. anitratum	5	5	6.9	3	0.60
Hemophilus influenzae	6	4	5.5	0	0.0
Escherichia sp.	6	2	2.7	1	0.5
Proteus sp.	3	2	2.7	2	1.0

* Penicillin Suppression-Unmasking Index = Column 5/Column 3.

† Does not include two specimens which yielded Klebsiellae on plates of penicillin-containing media but not on plates of penicillin-free media.

from the postpenicillin sputum only. *Micrococcus pyogenes* var. *aureus* (coagulase-positive) occurred in two patients prior to therapy, but persisted after treatment in the sputum of only one. Other bacterial species, including *Hemophilus influenzae* and *M. pyogenes* var. *albus*, were encountered rarely and are not considered in this analysis.

The aerobic bacterial pathogens isolated from the group of 104 sputa originating from 73 patients are listed in table 2. With reference to Klebsiellae, 20 of the 104 specimens examined (19.2%) yielded these organisms on either penicillin-containing media or penicillin-free media, or both. In 18 specimens Klebsiellae were found on the routine plates when they were also present on the penicillin plates. Only two specimens failed to show these bacilli on the routine plates when they did occur on the penicillin-containing plates. In one of these instances the organisms developed in the presence of both penicillin concentrations (i.e., one unit per milliliter

and five units per milliliter). In the second instance they grew out only on the plate containing the higher penicillin concentration. Superficially these two occurrences might be interpreted as illustrative of a "Klebsiella-unmasking effect" of penicillin. Consideration of other data in table 2, however, suggests the possibility of alternative interpretations. Column 3 lists the number of patients whose sputum yielded the indicated bacterial species when examined with penicillin-free media, column 5 lists analogous data obtained with penicillin-containing media. The ratio column 5: column 3 we have designated "penicillin suppression-unmasking index" (PSUI). The value of PSUI shown in column 6 is a measure of the number of strains of the indicated organism susceptible to the penicillin concentrations used in the media, and the relative frequency of occurrence of the species on penicillin media in comparison with that on penicillin-free media. On the basis of the PSUI value, the organisms listed in table 2 fall into one of four broad groups:

Group A: PSUI values 0.1 or less. This group included *D. pneumoniae, H. influenzae,* and *Str. viridans,* organisms which were uniformly or almost uniformly susceptible to the penicillin concentrations used. They rarely occurred on penicillin-containing media and, when they did, were also present on penicillin-free media.

Group B: PSUI values 0.1 to 0.99. This group included strains of *M. pyogenes* var. *aureus,* Escherichia, Paracolobactrum and *B. anitratum.* Among these were individuals which varied as to penicillin sensitivity and, although some did not appear on penicillin-containing media, it was possible to isolate them in every instance from the penicillin-free plates.

Group C: PSUI value 1.0. Included in this group were penicillin-resistant Pseudomonas species and Proteus species which were isolated from both penicillin-free and penicillin-containing media.

Group D: PSUI values greater than 1.0. Included only Klebsiellae, a group which was penicillin-resistant and appeared to occur more frequently on plates with penicillin than on those lacking it.

The fact that there were only two instances in which gram-negative bacilli became apparent following suppression of the susceptible sputum flora by penicillin, and that in both instances the emerging types were Klebsiellae to the exclusion of other penicillin-resistant species seemed odd. A number of explanations present themselves:

1. The sputum examination, specifically that portion of it employing penicillin plates, was designed to "pinpoint" Klebsiellae, and consequently caused selective isolation of these organisms. This possibility was discarded, since we are aware of no evidence to support the belief that penicillin concentrations of either one unit per milliliter or five units per milliliter are more effective in revealing Klebsiellae by suppression of susceptible flora than they are in revealing other enterobacilli (e.g., Pseudomonas, Proteus, etc.).

2. The procedure used for routine sputum examination is too crude to permit reproducible findings of the composition of its microflora, particularly with reference to those components present in comparatively small numbers. It has been demonstrated that there may be considerable variation, both qualitative and quantitative, in the organisms contained in replicate samples of a sputum specimen, and that examination of a single small portion of it may result in findings which are not representative.[14]

3. Sputum flora may vary in its composition within relatively short intervals of time in patients who are not receiving antimicrobial therapy. Consideration of the findings of all the sputum examinations on the two patients who showed an apparent "Klebsiella-unmasking" lends support to this possibility. Case 1 was hospitalized on October 1, 1956, and sputum examination on admission revealed *D. pneumoniae, Str. viridans* and Neisseria sp. A second specimen, examined on October 3, 1956, showed the same organisms in addition to a yeast. A third sputum, on October 4, 1956, yielded findings identical to the one on the preceding day except that a Klebsiella sp. now replaced the yeast. Case 2 was hospitalized on September 26, 1956. Three consecutive sputum specimens, which were cultured beginning October 2, 1956, revealed identical flora with the exception of the specimen on October 3, which showed a Klebsiella sp. in addition. These day-to-day floral changes without obvious cause diminish the significance of the apparent penicillin effect in such a small number of cases.

On the basis of the foregoing, it is suggested that penicillin does not usually reveal the presence of Klebsiellae or other gram-negative, penicillin-resistant bacilli in sputum when these organisms cannot be demonstrated on routine culture plates (penicillin-free), such as were used in this study.

The 104 sputum specimens came from 73 patients, 15 of whom showed Klebsiellae, corresponding to a prevalence of 20.5%. Data on antibiotic therapy among these patients were available in 14 cases; seven (50%) were not receiving antimicrobial therapy at the time of sputum collection. Information on antibiotic therapy was obtained in 50 patients whose sputum failed to reveal Klebsiellae, and 28 (56%) were not receiving antimicrobial drugs.

Discussion

Prior to a discussion of the implications of our experimental results, it seems necessary to state briefly what we mean when we refer to an organism as being a Klebsiella, or belonging to the Klebsiella group. The necessity for definition is dictated by our experience that among clinicians the name Klebsiella connotes the Friedländer bacillus or *K. pneumoniae*. As pointed out by us and others [1-8] elsewhere, this viewpoint is too narrow and is no longer tenable. A considerable amount of study during the past quarter-century has yielded unequivocal evidence that the classic strains of the genus Klebsiella, including the Friedländer bacillus, are indistinguishable by morphologic and biochemical criteria from the classic nonmotile mem-

bers of the genus Aerobacter, typified by *Aerobacter aerogenes*. As a consequence, it has been recommended [1, 2] that these and related strains previously assigned to either of these two groups should be allocated to a single genus which, on the basis of priority, should properly be called "Klebsiella." The group as a whole possesses morphologic and biochemical characteristics which serve to differentiate it from other groups of gram-negative bacilli. In addition, it was also shown that differentiation of individual strains within the group could be accomplished serologically, most practically on the basis of differences in capsular antigen reactivity with homologous antiserum.[2] The use of proper names in identifying different strains was replaced by a system employing Arabic numerals. Thus, the classic *K. pneumoniae* type A is designated as Klebsiella type 1, *K. pneumoniae* type B as Klebsiella type 2, etc. To the best of our knowledge, a total of 77 capsular types of Klebsiella have been described so far.

In consideration of the above, the term Klebsiella as used herein refers to a group of serologically related gram-negative, nonsporing, nonmotile bacilli which usually possess capsules, form mucus, and exhibit a more or less defined pattern of biochemical reactions. Within this large group are to be found those organisms commonly thought of as classic Friedländer bacilli and *A. aerogenes*.

It has been observed frequently that penicillin therapy, under appropriate conditions, may be attended by remarkable qualitative and quantitative alterations in the bacterial population normally indigenous to the respiratory tract. The qualitative changes consist of replacement of the penicillin-susceptible types by resistant organisms, very often including representatives of the enteric group. These changes are temporary; upon cessation of therapy, the "normal" flora becomes reëstablished after a variable period of time. This sequence of events has been attributed to a direct causative effect of penicillin.

Our data do not offer evidence in favor of this concept as a satisfactory explanation for the frequency of appearance of Klebsiellae or other gram-negative bacilli in the sputum of patients hospitalized at this institution. In the first place, the results fail to show an unequivocal association between the occurrence of these organisms in sputum and penicillin therapy. This is exemplified by the inability to demonstrate sputum conversion to a predominantly gram-negative bacillary flora in any of the 14 patients to whom penicillin was given. Furthermore, among the 73 unselected patients whose sputa were examined without benefit of prior knowledge of which of these individuals had received antibiotics, the number from whom Klebsiellae were isolated was equally divided between those who received antibiotics and those who did not. Among 50 patients of the group whose sputum failed to yield these bacteria, one-half had received antibiotics and one-half had not. Second, no evidence could be developed in support of the thesis that Klebsiellae are present in the sputum of untreated patients in such small numbers that their presence is not apparent as a result of overgrowth by

more prolific members of the microbial community. This is evident from the in vitro tests utilizing isolation plates with and without penicillin. Consequently, it seems unlikely that the source of the higher serotype Klebsiellae as encountered by us in sputum can be explained solely or adequately on the basis of a selective penicillin-inhibitory effect the result of which is the establishment of a replacement microflora.

Failure of our results to demonstrate a cause-and-effect relationship between penicillin therapy and appearance of higher serotype Klebsiellae and other gram-negative bacilli in sputum at first glance may seem to be at variance with the results of other workers. This contradiction may be more apparent than real, since it is not improbable that both viewpoints may be correct, provided due consideration is given to certain factors.

A survey of the literature from 1940 to the present, dealing with the effect of penicillin on respiratory tract flora, reveals many references to studies reporting the appearance of enteric bacilli in nasal, nasopharyngeal and oral secretions during and following use of this antibiotic.[4-10] In contrast, we could find only one publication describing experiments intended to determine the effect of penicillin on the *sputum* flora,[15] but this study was limited to a small number of out-patients. Obviously, the belief that penicillin is responsible for the appearance of gram-negative bacilli stems largely from observations of changes in microbiologic composition of the secretions of the *upper* respiratory tract, and in reality *there is little if any experimental evidence to sustain the belief that the drug produces the same or similar effects upon the microflora of the lower respiratory tract.* In the absence of this evidence it is hazardous to assume that, because penicillin has been observed to alter the normal flora of the upper respiratory tract in a way which causes the emergence of gram-negative bacilli, it will affect the sputum flora in the same manner. The studies of Brown et al.[16] on the bacterial flora encountered in bronchial aspirates, sputa and nasopharyngeal secretions of patients with chronic bronchopulmonary disease have shown that the pathogenic flora of sputum differs from that of the nasopharyngeal secretions. Barach et al. have pointed out that intramuscular injections of penicillin in patients with chronic bronchitis, bronchiectasis and lung abscess are not generally accompanied by the appearance of demonstrable antibiotic levels in sputum.[17] If this is true, the probability of effecting marked changes in the sputum flora would appear to be significantly reduced.

The problem of determining what constitutes the "normal" flora of a sputum and how it is affected by penicillin is complicated by the difficulty of obtaining a specimen known to be truly representative of the total bacterial population. May [14] has emphasized the inadequacy of results obtained from examination of single routine specimens by demonstrating that bacteria are distributed unevenly in sputum. While this may account for some of the observed variation, it is not the complete answer, since he was also able to show variations in sputum flora of the same patient in different specimens. Rawlings [18] proposed homogenization of sputum by pancreatin as a method

for obtaining representative cultures. Even if these technical difficulties were overcome, there would still exist the need for careful studies providing for variations in factors such as dosage and duration of penicillin administration in relation to sputum examinations, etc., before a factual assessment could be made.

In view of the foregoing considerations, penicillin therapy does not appear to supply an adequate explanation for the common isolation of Klebsiellae in the sputum of patients at this institution. Therefore, we have considered host characteristics. In comparing patients from whom Klebsiellae have been isolated with other patients on the same wards from whom these organisms could not be isolated, we have so far found no significant differences between these groups with respect to age, sex, race, the presence of pulmonary disease, or the presence of chronic bronchopulmonary disease.

The possibility of a nosocomial reservoir cannot be ignored in view of the finding in a previous survey at this institution that nasopharyngeal secretions of 2% of 200 ward personnel and slightly more than 8% of 97 patients without overt respiratory tract disease yielded Klebsiellae. Lepper [19] has done a small epidemiologic study of four tracheotomized patients in a single room and found that almost all of the strains of bacteria which appeared in the tracheal secretions of these patients were found about the person of one of the personnel who had entered the room the day before. Studies of this sort will be helpful in determining the nosocomial importance of higher serotype Klebsiellae. Recent experiences with the problem of staphylococcus infections acquired in hospitals lead one to believe that the situation is in all probability not peculiar to any one bacterium. There is an ever-increasing awareness that antibiotics play a role in the gradual selection of organisms in the hospital environment over a period of time, so that resistant organisms become progressively more common. As a result, the opportunities for such organisms to be passed back and forth from personnel to patient to personnel are increased. Thus, antibiotics have shifted clinical importance from the once dreaded pneumococcus and beta hemolytic streptococcus to the staphylococcus and the gram-negative enteric bacilli. It behooves us to resume every precautionary measure to prevent the spread of these infective agents if we are not to see our hospitals revert to the days of Semmelweis.

Summary and Conclusions

Previous experience involving frequent encounters with higher serotypes of Klebsiellae in sputum from patients with respiratory tract disease and occasional failure to establish an etiologic relationship between these organisms and the patient's disease motivated an attempt to determine the source of origin of these bacilli. In addition, it was believed that interpretation of their clinical significance would be facilitated if this information was available.

An approach to the investigation was suggested by an impression received from an earlier study, namely, that the appearance of higher serotypes of Klebsiellae in sputum was possibly related to antibiotic therapy, specifically, penicillin. This possibility gained strength in the light of the generally accepted hypothesis that penicillin therapy is responsible for altering the microflora of the upper respiratory tract in such a way that the normally indigenous organisms are replaced by penicillin-resistant, gram-negative bacilli.

Clinical and laboratory experiments were performed to evaluate the validity of this impression. Results of the clinical experiment failed to establish an association between penicillin therapy and the appearance of gram-negative bacilli (including Klebsiellae) in the sputum of 14 patients to whom penicillin was given. A similar conclusion was reached following evaluation of a group of 73 unselected patients whose sputa were examined without benefit of prior knowledge of their antibiotic status. The laboratory experiment indicated that bacteriologic examination of 104 sputum specimens on media containing penicillin does not usually reveal the presence of these organisms when they cannot be demonstrated on routine, penicillin-free culture media.

Because of these results, it seems unlikely that the source of the higher serotypes of Klebsiellae as encountered by us in sputum can be explained solely or adequately on the basis of a selective penicillin-inhibitory effect, the net result of which is the establishment of a replacement flora. The apparent variance of our results with those reported by other investigators is discussed.

The relationship of certain host characteristics to the appearance of higher serotypes of Klebsiellae in sputum is also discussed.

The role played by antibiotics in the gradual selection of organisms in a hospital environment and the consequent establishment of a nosocomial reservoir as applied to Klebsiellae are mentioned briefly.

SUMMARIO IN INTERLINGUA

Le presente studio esseva programmate pro determinar le effecto de penicillina super le flora sputal in vivo e in vitro, con referentias particular a species de *Klebsiella*. Le basse typos capsular de *Klebsiella*, i.e. typos 1 a 4, es pauco commun, sed in multe casos illos es clarmente pathogenos primari de infectiones del vias respiratori, proque illos es jam presente in le vias respiratori quando le patiente as admittite al hospital, e lor presentia es frequentemente associate con destructive morbos pulmonar. Del altere latere, klebsiellas de plus alte typos es multo plus commun in le sputo de patientes hospitalisate, sed usualmente illos appare un certe tempore post le admission del patiente, e il sembla que illos ha rarmente un rolo como pathogenos primari. Illos es incontrate con le mesme frequentia in patientes qui non recipe antibioticos como in patientes qui recipe antibioticos.

Il ha essite postulate que bacillos negative al Gram existe in le vias respiratori in numeros occultemente micre e deveni le organismos predominante quando le indigene bacterios respiratori es inhibite per antibioticos. In le caso special de penicillina e

Klebsiella, iste hypothese non esseva supportate per le sequente duo experimentos: (1) Le administration de penicillina in le dosage usual a 14 patientes non resultava in un conversion del flora del sputo in un forma con predominantia de bacillos negative al Gram. E (2), penicillina non revelava—a generalmente parlar—le presentia de bacillos negative al Gram in sputos in que illos non esseva presente in culturas routinari.

Le supra-presentate consideratione pare indicar que le frequente apparition del typos plus alte de species de *Klebsiella* in le vias respiratori de hospitalisatos resulta de un dissemination nosocomial plus tosto que del effecto de therapia antibiotic super le microflora.

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CARCINOMA OF THE COLON UNDER THE AGE OF 40 *

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Carcinoma of the colon is a common disease. What is not appreciated is that it is one of the most common malignant growths found in young adults. Although there is ample literature dealing with colonic carcinoma, no report has been published concerning this disease in the younger age groups. On the basis of a recent experience our suspicion was raised that this disease might be a more malignant process in young adults. We have therefore conducted a review of the cases of colonic carcinoma seen at the St. Louis University Hospitals in order to investigate this point.

Material for Review

The cases selected for this study were those patients with pathologically proved colonic carcinoma seen at the St. Louis City Hospital, Firmin Desloge Hospital, and the St. Louis Veterans Administration Hospital from January, 1950, to May, 1957. Material extracted from the charts includes age, sex, location of lesions, presenting symptoms, and course following diagnosis.

Results

Of the 840 cases of carcinoma of the large bowel, 33 were under the age of 40 years, an incidence of 4%. This figure varied widely from one hospital to another: at St. Louis City Hospital it was 1.9%, at Firmin Desloge it was 3%, and at the Veterans Administration Hospital it was 10%. There was a total of 19 males and 13 females. However, in the two hospitals dealing primarily with mixed populations the ratio was 13 females to four males.

The locations of the lesions are shown in table 1. The presenting symptoms are tabulated in table 2. Five of the patients with colonic carcinoma presented as acute abdominal emergencies, two as appendicitis, and three as bowel obstructions.

Course and Outcome

There were 13 cases of rectal carcinomas. One patient is excluded from the rectal group since he also had a symptomatic cecal carcinoma and for

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the purpose of tabulation is included in the colon group. The age range of the 12 patients studied was from 23 to 39 years. There were eight males and four females, all white. Excluding the patient with two lesions, 12 rectal carcinomas have been followed. Eight of these patients (66%) died three to 58 months after diagnosis. The remaining four patients (33%) are alive and well from five to 24 months after the diagnosis was made. Of these four, the disease in two was a malignant polyp discovered on routine examination.

There were 20 patients with colon carcinomas other than rectal. One was lost to follow-up, and this patient is presumed to be dead. Thirteen (65%) died within three to 28 months after they were seen. Two patients

TABLE 1

Location of Lesion	Number of Cases	%	Males	Females
Rectum*	13	40	9	4
Sigmoid	12	36	5	7
Transverse colon	5	15	4	1
Cecum*	2	6	2	0
Unknown	1	3	0	1
Totals	33	100	20*	13

* One man had two primary carcinomas, one in the rectum, the other in the cecum, and is included in both.

are alive but have metastatic disease six and 24 months after the onset, and one patient is alive six months after operation for a ruptured cecal carcinoma. The remaining three patients are alive and well from one to four years postoperatively.

Thus, of a total of 32 patients with colon malignancy, 25 (78.3%) are dead or are expected to die of their disease in less than five years, 16 having died within 18 months. Seven patients are living without disease from five to 48 months postoperatively. If one presumes that all seven of these patients will live five years or more, the very best the five-year survival rate can be is 21.7%.

DISCUSSION

Carcinoma of the colon is one of the most common malignancies seen in young adults, exceeded at the Veterans Administration Hospital only by the leukemia-lymphoma group, carcinoma of the skin and carcinoma of the respiratory tract. It was the most common carcinoma in young adults seen at the St. Louis City Hospital. At Firmin Desloge Hospital it was exceeded only by lung, breast and bladder malignancies.

It is generally accepted that approximately 10% of colonic carcinomas occur in patients under the age of 40.[4, 7, 14, 15] However, there was a wide variation in the incidence in this age group in the three hospitals studied. The very low figure of 1.9% at the St. Louis City Hospital may be related

to the fact that in the hospital population one third of the patients are over 70 years and two thirds over 50 years, whereas at the Veterans Administration Hospital two thirds of the patients are under 50 years.

Carcinoma of the colon is more common in the male than in the female, the approximate ratio being 1.5 : 1.[2, 4, 7, 14] Our findings are in essential agreement with this. However, it should be noted that in the two hospitals with a mixed population there was a preponderance of females over males, 13 to four. This may be a corroboration of Dukes's finding that rectal carcinoma occurs at an earlier age in females than in males.

The distribution of the lesions in this group of patients is not significantly different from that of carcinoma of the colon in all age groups. Approximately 75% of the carcinoma occurred in the rectum and sigmoid.

TABLE 2

Symptoms	Rectum (12 patients)	Colon (20 patients)
Melena	10	9
Pain	6	11
Constipation	4	12
Diarrhea	3	4
Weight loss (average 20 pounds)	4	12
Duration of symptoms before admission (average)	4 mos.	8 mos.

The symptoms of which the patients complained were similar to those of any large group of cases of colonic carcinoma (table 2). Gross and occult blood was more common in patients with rectal carcinoma, whereas constipation and weight loss were more frequent in the patients with colonic lesions. The incidence of pain and diarrhea was the same regardless of the location of the lesion. The duration of symptoms varied from a few hours up to three years, and in general symptoms had been present for a longer time in patients with colonic lesions, perhaps because copious bleeding per rectum in many of the patients with rectal carcinoma prompted earlier medical care. Five patients were admitted as acute abdominal emergencies; two of these had ruptured cecal carcinomas, and three had large bowel obstructions secondary to their disease.

The survival rate reported herein is certainly discouraging because it represents the results of diagnosis and therapy in a modern era of medicine. Fifteen years ago encouraging reports were frequent in the medical literature, and five-year survival rates were given as approximately 50%.[1, 5, 18] Some recent authors estimate that only one third of the patients will survive five years when an unselected series is analyzed.[4, 12, 14, 15, 17] However, a large number of current reports continue to write of the over-all five-year survival rate as approximately 50%.[2, 3, 8, 9, 10, 11, 16] Our rate of survival in this group of young patients was only 21%, a value significantly lower than that

accepted generally. It is difficult to explain the very poor prognosis in our group of young patients. Their symptoms had been present for the same period of time as in the older patients, and corresponded to the time intervals reported in other series. Surgery was not unduly delayed in any individual. As a group these patients are better operative risks than their older counterparts and, although reported operative mortality rates are generally quite high, varying from 3.0 to 9.6%,[4, 8, 12, 15, 16] there were no operative deaths in this series. The absence of lymphatic or vein invasion at the time of surgery was of little prognostic value. Two patients who had had no evidence of spread at surgery died of metastatic disease within one year. One would expect the survival rates to be better for the younger age group patient than for the group as a whole, unless colonic carcinoma is more fulminating in the younger individual.

It has generally been accepted that cancer in younger age groups tends to be a more malignant process, though this has recently been denied.[4, 6, 13] Dukes, referring to lesions of the rectum, said, "Carcinoma gives rise to metastases more rapidly in the young patients than in the old." [7]

Conclusion

The five-year survival rate in this series of 32 patients was less than 21% at best. This indicates that carcinoma of the colon is a formidable disease which apparently has an accelerated course in patients under the age of 40 years.

The duration of symptoms prior to surgery did not seem to be an important factor in patient survival. The excellent prognosis in two cases of malignant polyp found by routine sigmoidoscopy contrasts sharply with the poor prognosis of patients with symptoms, regardless of duration.

Summario in Interlingua

Esseva effectuate un revista del casos de carcinoma del colon in adultos de minus que 40 annos de etate, vidite al hospitales del Universitate St. Louis inter januario 1950 e maio 1957. In omne casos le diagnose de malignitate del lesion colonic esseva basate super un examine pathologic.

Pro le periodo indicate, un total de 840 casos de carcinoma del colon esseva trovate in le archivos. In 33 casos (4%), le patiente habeva minus que 40 annos de etate. Inter istes, 19 esseva mascule e 13 feminin. Le sito del lesion primari esseva le recto in 12 casos, le sigmoide in 12, le colon transverse in cinque, illo esseva incerte in un caso, e un patiente habeva lesiones co-existente in le recto e le ceco.

Melena, dolores, constipation o diarrhea, e perdita de peso esseva le symptomas primari. Cinque patientes esseva initialmente vidite sub conditiones de urgentia con acute attaccos abdominal. In duo del cinque, appendicitis esseva supponite; in le altere tres, obstruction intestinal. Le duration del symptomas ante le diagnose amontava a un valor medie de quatro menses in le casos de carcinoma del recto e de octo menses in le casos de carcinoma a sito non-reactal.

Dece-duo del casos de carcinoma rectal remaneva sub observation. Qcto de illos (66%) se terminava in morte per metastases inter tres e 58 menses post le

diagnose. Le remanente quatro patientes de iste gruppo (33%) vive, inter cinque e 24 menses post le intervention chirurgic. In duo, isolate polypos maligne esseva excidite. Dece-nove del casos de carcinoma colonic non-rectal remaneva sub observation. Dece-tres de illos (65%) se terminava in morte per metastases inter tres e 28 menses post le intervention chirurgic. Duo patientes de iste gruppo ha demonstrabile metastases, sex e 24 menses post le operation, e tres vive sin metastases, sex a 48 menses post le diagnose. Assi, solmente septe del 32 patientes tenite sub observation vive sin metastases, cinque a 48 menses post le resection. Si nos suppone que omne iste septe patientes supervive cinque annos, le procentage del superviventia quinquenne non pote exceder 21,7. Isto pare indicar que le curso de carcinoma colonic es accelerate in juvene adultos.

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APLASTIC ANEMIA: AN ANALYSIS OF 50 CASES *

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INTRODUCTION

SINCE Ehrlich's [1] original description of aplastic anemia in 1888, many names have been applied to this type of anemia: bone marrow failure,[2] aleukia hemorrhagica,[3] aregenerative anemia,[3] panmyelophthisis,[3] marrow insufficiency,[4] toxic paralytic anemia,[5] progressive hypocythemia,[6] hypoplastic anemia,[7] refractory anemia [8] and adynamic anemia.[9] The Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-forming Organs [10] has recommended the term "hypoplastic normocytic or macrocytic anemia, due to unknown cause."

None of the suggested names is entirely satisfactory. The chief objection to the term "aplastic anemia" is the fact, first pointed out by Blumer [11] in 1905 and later amplified by others,[6, 12-14] that a considerable number of patients who have peripheral blood findings and a clinical course consistent with aplastic anemia have bone marrows which are normocellular or hypercellular rather than hypocellular. However, since it has been repeatedly pointed out that bone marrow function and bone marrow morphology may correlate poorly,[6, 15-18] it might be permissible to use the term "aplasia" to denote either morphologic or functional inadequacy of the bone marrow. The nomenclature of this type of anemia will probably remain unsatisfactory until more is learned about the etiology and pathologic physiology of the disorder. Meanwhile, it would seem least confusing to use the term "aplastic anemia," since it has the longest and most common usage.

Whether patients with this condition represent variations of a single disturbance or form a heterogeneous group of different entities is not clear. It is clear that this condition is an ever-recurring problem in hematology, and one which some observers feel is increasing in frequency.[19] For this reason it is hoped that an analysis of a large number of patients with this disorder might give some clues which will be helpful in approaching some of the many difficult problems presented by this type of anemia.

SELECTION OF PATIENTS

All of the patients in this study were seen by members of the staff of the University of Virginia Hospital between the years 1933 and 1956, and

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all but nine were seen by one of us (B. S. L.). All of the 15 living patients have been followed for at least a year, and only two have been lost to follow-up.* The other 35 were followed to the time of death, and autopsies were performed on 14. Table 1 gives pertinent data on all 50 patients in this series, and all subsequent case numbering is based on this table.

The peripheral blood and bone marrow of each patient were examined and in each instance there was evidence of defective blood production. A clinical diagnosis of aplastic anemia was made in every case except one (case 50), in whom the diagnosis was made for the first time at autopsy. Patients were excluded from this study if they had chronic infection, malignancy, malnutrition, renal disease or liver disease, conditions known to depress bone marrow functions, or if they had been treated with agents such as nitrogen mustard derivatives, urethane and irradiation. Patients with myelofibrosis and myeloid metaplasia were also excluded. Patients who had been exposed to various toxins or drugs which do not regularly produce bone marrow depression were not excluded from this series; nor were patients excluded who had a hemolytic element as long as inadequate blood production was thought to be the predominant defect.

Incidence

Table 2 shows a comparison of the age, sex, racial and toxic incidence in 12 reported series of patients with aplastic anemia, including our own. An analysis of these 364 cases reveals the following findings.

Age: The age at the onset of illness varied from six months to 82 years, and 65.5% of the patients had the onset of their illness under the age of 51. In our series there were 10 patients under 20 years of age; from 20 to 39, 13 patients; 40 to 59, 13 patients; and older than 59, 14 patients. There were approximately the same number of patients in each 20-year period.

Sex: Fifty-seven per cent of the entire group were males, and 70% in our series were males. Vaughan's [17] observation that women are less likely to acquire this disease after the age of 50 is supported by these figures, which show 102 of the 220 patients under 50 (46.5%) to be women, while only 42 of the 116 over 50 (36%) were women. The male-to-female ratio was 1.2: 1 in patients younger than 50, and 1.8: 1 in patients older than 50.

Race: The race was known in 196 of these patients, and only six (3%) were Negroes.

Toxins: There was a history of toxic exposure in 21.5% of the whole group and in 14% of our series.

Family History: In our series, nine patients gave a history of anemia in other members of the family, but this was documented in only three. Cases 10 and 49 were brothers with Fanconi's syndrome (congenital hypoplastic

* Case 2 was lost to follow-up in April, 1955, after having been followed for eight years and three months. Case 7 was followed for two years and 10 months and when last seen, in July, 1954, had been in complete remission for one year.

TABLE 1

Pertinent Data on 50 Patients with Aplastic Anemia

Case	Sex	Age at Onset	Etiology	Presenting Type of Bone Marrow Cellularity	Presenting Type of Peripheral Blood	Cause of Death	Duration of Illness	Comment
1. S. A.	F	36	Idiopathic	Hypo.	Pancytopenia	Living	3 yrs. 3 mo.*	Prominent hemolytic element to anemia, leukocytes and platelets returned to normal following splenectomy, anemia did not improve.
2. J. B.	M	20	Idiopathic	Hypo.	Pancytopenia	Lost to follow-up	8 yrs. 3 mo.†	Long duration with pancytopenia.
3. W. C.	M	65	Idiopathic	Hypo.	Pancytopenia	Living	1 yr. 5 mo.	Spontaneous remission.
4. M. H.	F	62	Idiopathic	Hypo.	Anemia	Living	9 yrs.	Complete remission after splenectomy.‡
5. H. H.	M	51	Idiopathic	Hyper.	Anemia	Living	17 yrs. 6 mo.	Long duration with prominent hemolytic element.
6. E. J.	M	28	Idiopathic	Hyper.	Pancytopenia	Living	3 yrs. 10 mo.	Hemolytic element present.
7 D. P.	F	30	Idiopathic	Hypo.	Pancytopenia	Lost to follow-up	2 yrs. 10 mo.†	Complete remission after cortisone.
8. T. S.	F	55	Phenyl-butazone	Hypo.	Anemia	Living	1 yr. 4 mo.	Complete recovery.
9. G. S.	M	25	Mesantoin	Hypo.	Pancytopenia	Living	1 yr. 9 mo.	Complete recovery.
10. P. T.	M	9	Idiopathic	Hypo.	Pancytopenia	Living	4 yrs.	Fanconi's syndrome.
11. B. W.	M	36	Idiopathic	Hyper.	Pancytopenia	Living	4 yrs. 4 mo.	Marked thrombocytopenia which improved on cortisone.
12. C. G.	M	82	Idiopathic	Hypo.	Anemia	Living	1 yr. 3 mo.	Complete remission after prednisone with relapse when drug discontinued.
13. S. C.	M	73	Idiopathic	Hypo.	Pancytopenia	Living	4 yrs. 9 mo.	Complete remission after cortisone.
14. B. H.	M	52	Idiopathic	Hypo.	Pancytopenia	Living	2 yrs.	Partial remission after splenectomy.
15. C. P.	M	9	Idiopathic	Hypo.	Pancytopenia	Living	1 yr. 3 mo.	May represent congenital anemia.
16. H. B.	M	62	Benzol	Hypo.	Pancytopenia	Unknown	6 yrs.	Exposed to benzol as an ammunition inspector.
17. B. B.	F	34	Idiopathic	Hypo.	Pancytopenia	Unknown	6 mo.	Rapid course.
18. G. B.	M	78	Idiopathic	Hypo.	Pancytopenia	Staph. septicemia	8 mo.	Septic course.
19. M. C.	F	1?	Idiopathic	Hypo.	Pancytopenia	*E. coli* septicemia	6 yrs.	Partial spontaneous remission lasting four years.
20. T. D.	M	49	Benzol	Hypo.	Pancytopenia	*A. aerogenes* septicemia, pulmonary embolus	5 mo.	Painter exposed to large amounts of Varosal, a benzol containing solvent.
21. J. G.	M	54	Benzol	Hypo.	Anemia, leukopenia	Congestive failure, pneumonia	1 yr. 10 mo.	Burned old paint cans containing paint thinner and paint remover, autopsy.
22. K. H.	F	16	Idiopathic	Hypo.	Pancytopenia	Hemorrhage	4 mo.	Rapid course not improved by splenectomy

* Duration of illness in living patients based on follow-up to April 1, 1957.
† Duration of illness in patients lost to follow-up based on last follow-up.
‡ Reported in detail as a case report.

TABLE 1—(*Continued*)

Case	Sex	Age at Onset	Etiology	Presenting Type of Bone Marrow Cellularity	Presenting Type of Peripheral Blood	Cause of Death	Duration of Illness	Comment
23. J. H.	M	79	Idiopathic	Hypo.	Pancytopenia	Unknown	5 mo.	Rise in platelet count and less bleeding after cortisone.
24. G. H.	F	25	Idiopathic	Hypo.	Pancytopenia	Intracranial hemorrhage	3 yrs.	Decreased bleeding tendency after cortisone, autopsy.
25. T. J.	M	65	Idiopathic	Hypo.	Anemia, leukopenia	Acute leukemia, Klebsiella pneumonia	4 yrs. 6 mo.	Developed acute myelocytic leukemia terminally, autopsy.‡
26. L. J.	F	11	Idiopathic	Hypo.	Pancytopenia	Hemorrhage, sepsis	2½ mo.	Sudden onset and rapid course.
27. T. L.	M	43	Idiopathic	Hypo.	Anemia	Gram neg. septicemia	5 yrs.	Example of pure red cell involvement.
28. T. L.	F	36	Idiopathic	Hyper.	Anemia, thrombocytopenia	Intracranial hemorrhage	12 yrs.	Spontaneous remission lasting eight years, autopsy.‡
29. E. S.	F	4	Chloramphenicol	Hypo.	Pancytopenia	Hemorrhage, septicemia	2½ mo.	Took chloramphenicol prophylactically to prevent recurrent tonsillitis, autopsy.
30. B. R.	M	58	Arsenic fruit spray	Hypo.	Pancytopenia	Pseudomonas septicemia	2 mo.	Exposure to arsenical fruit spray, autopsy.‡
31. F. S.	F	69	Idiopathic	Hypo.	Pancytopenia	Hemorrhage	10 mo.	Generalized bleeding with severe thrombocytopenia
32. R. T.	M	54	Idiopathic	Norm.	Anemia	Pneumonia	14 yrs. 3 mo.	Long lasting partial remission after cortisone, autopsy.‡
33. D. W.	M	42	Idiopathic	Hypo.	Pancytopenia	Hemorrhage	20 yrs. 9 mo.	Long duration of pancytopenia in a eunuch, autopsy.‡
34. H. L.	M	30	Idiopathic	Norm.	Pancytopenia	Septicemia	8 mo.	Developed a noma of the cheek.
35. S. A.	F	54	Idiopathic	Hypo.	Pancytopenia	Intracranial hemorrhage	2 yrs.	Extensive purpura, autopsy.
36. B. G.	M	56	Idiopathic	Hypo.	Pancytopenia	Congestive heart failure	11 yrs.	Questionable remission following crude liver extract with subsequent relapse.
37. H. M.	M	71	Idiopathic	Hypo.	Pancytopenia	Unknown	1 yr. 3 mo.	Refused transfusions.
38. L. A.	M	68	Idiopathic	Norm.	Anemia, leukopenia	Unknown	4 yrs. 6 mo.	Bone marrow showed erythroid hypoplasia.
39. T. H.	F	71	Idiopathic	Hypo.	Anemia, thrombocytopenia	Septicemia, pneumonia	2 yrs. 4 mo.	Exogenous hemochromatosis at autopsy.
40. S. C.	M	59	Idiopathic	Hypo.	Anemia	Unknown	3 yrs. 6 mo.	Developed splenomegaly after multiple transfusions.
41. W. P.	M	63	Idiopathic	Norm.	Anemia, leukopenia	Unknown	4 yrs. 10 mo.	Atrophic testicles.

TABLE 1—(*Continued*)

Case	Sex	Age at Onset	Etiology	Presenting Type of Bone Marrow Cellularity	Presenting Type of Peripheral Blood	Cause of Death	Duration of Illness	Comment
42. J. B.	M	66	Idiopathic	Norm.	Pancytopenia	Intracranial hemorrhage	2 yrs. 3 mo.	Self-medication with multiple drugs prior to onset of illness.
43. R. M.	M	8	Idiopathic	Hypo.	Pancytopenia	Pneumonia	4 yrs.	Fanconi's syndrome.
44. O. H.	M	9	Idiopathic	Norm.	Pancytopenia	Intracranial hemorrhage	1 yr. 6 mo.	Illness followed a severe case of measles.
45. M. M.	F	16	Idiopathic	Norm.	Pancytopenia	Hemorrhagic pneumonia	8 yrs. 3 mo.	Long course with marked pancytopenia, autopsy.
46. H. B.	M	25	Idiopathic	Norm.	Pancytopenia	Hemorrhagic pneumonia	7 mo.	Hemolytic element to anemia, autopsy.
47. F. G.	M	32	Idiopathic	Hyper.	Pancytopenia	Unknown	1 yr. 3 mo.	Hemolytic element to anemia.
48. W. H.	M	43	Idiopathic	Hypo.	Pancytopenia	Hemorrhage	1 yr.	Transient improvement on cortisone.
49. W. T.	M	14	Idiopathic	Hypo.	Pancytopenia	Hemorrhagic pneumonia	3 yrs. 3 mo.	Fanconi's syndrome, autopsy.
50. C. C.	M	20	Idiopathic	Hypo.	Pancytopenia	*B. proteus* septicemia, intestinal hemorrhage	5 wks.	Thought clinically to have aleukemic leukemia but showed aplastic anemia at autopsy.‡

anemia associated with other developmental defects), while case 27 had a brother with pernicious anemia.

SYMPTOMS

The most common presenting symptom was weakness. When the anemia was corrected by transfusions many patients, especially those who had only red cell involvement, were symptom-free until the anemia recurred. Thirty-four per cent of the group noted a bleeding tendency such as epistaxis, menorrhagia, and bleeding from the gums. All of the patients with hemorrhagic manifestations had thrombocytopenia, but not all of the patients with thrombocytopenia had abnormal bleeding.

PHYSICAL EXAMINATION

The incidence of various abnormalities found on physical examination is shown in table 3. Many of these abnormalities developed late in the course of the illness.

Purpura or petechiae occurred in 48% of the patients, and all of these had thrombocytopenia with platelet counts of 60,000 per cubic millimeter (indirect method) or less. It is of interest that there were 15 patients with

TABLE 2

Comparison of the Age, Sex, Racial and Toxic Incidence in 12 Series of Patients with Aplastic Anemia

Authors	No. of Cases	Sex		Age at Onset					Race		Toxic History	
		M	F	Youngest	Oldest	Average Age	No. Less Than 51	No. Over 50	W	N	Positive	Negative
*Smith,[20] 1918	62	32	30	2	68	29	54	8	—	—	—	—
Thompson et al.,[6] 1934	13	12	1	25	70	46	8	5	13	0	3	10
January and Fowler,[21] 1940	19	13	6	12	70	35	15	4	—	—	6	13
Bomford and Rhoads,[5] 1941	66	34	32	6 mo.	72	37	46	20	66	0	17	49
Vaughan,[17] 1942	34	18	16	10 mo.	75	—	23	11	32	2	10	24
Davidson et al.,[22] 1943	16	7	9	21	72	61	6	10	—	—	4	12
Boon and Walton,[23] 1951	25	13	12	13	74	39	16	9	—	—	7	18
Spaet et al.,[9] 1951	19	9	10	4	73	47	9	10	—	—	4	15
Adams,[24] 1951	27	15	12	5	75	43	0	0	—	—	3	24
**Loeb et al.,[25] 1953	7	5	2	17	64	46	2	5	7	0	0	7
*Tsai and Levin,[26] 1957	26	15	11	20	67	46	14	11	24	2	4	22
Mohler and Leavell, 1957	50	35	15	4	82	43	27	23	48	2	7	43
Total No.	364	208 (57%)	156 (43%)				220 (65.5%)	116 (34.5%)	190 (97%)	6 (3%)	65 (21.5%)	237 (78.5%)

* Collected series of cases.

** Cases with myelosclerosis and myeloid metaplasia were excluded from this series.

platelet counts that ranged from 10,000 to 95,000 per cubic millimeter who had neither purpura nor petechiae. Retinal hemorrhages were observed in 18 patients, and two of these had normal platelet counts and normal blood pressures. Diffuse brown or brownish gray pigmentation was found in 24% of the patients, and an additional five patients had scattered areas of brown pigmentation. Three of these patients had Fanconi's syndrome (cases 10, 43 and 49), while in the other two (cases 44 and 45) anemia was discovered early in life—at the ages of nine and 16, respectively.

Twenty-four per cent of the patients developed significant lymphadenopathy during the course of their illness, and the spleen was palpable in 34%. The spleen was enlarged (over 150 gm.) in nine of 14 autopsied patients, and in four of these patients it was not palpated prior to death. The size of the spleens which were not palpated ranged from 170 gm. to 270 gm., while the spleens which were palpated ante mortem ranged in

TABLE 3

Pertinent Physical Abnormalities Noted in 50 Patients with Aplastic Anemia During the Course of Their Illness

Physical Finding	No. of Patients	Per Cent
Grayish-brown skin pigmentation	12*	24
Purpura or petechiae	24	48
Retinal hemorrhages	18	36
Significant lymphadenopathy	12	24
Splenomegaly	17	34
Hepatomegaly	16	32
Testicular atrophy	8	24

* In addition 5 patients had scattered areas of brown pigmentation.

weight from 365 gm. to 770 gm. at autopsy. The liver was felt in 32% of the patients, and at autopsy hepatomegaly (over 1,500 gm.) was present in all but two of the 14 patients, but was not detected clinically in four patients whose livers ranged in size from 1,540 gm. to 2,560 gm. The size of the livers felt ante mortem varied from 1,700 gm. to 2,600 gm. at autopsy. A possible factor in the higher incidence of enlargement of the lymph nodes, spleen and liver in this series of patients than in most other series reported previously may be the greater use of transfusions in recent years, as half of the autopsied patients showed increased amounts of hemosiderin in the reticuloendothelial organs (table 4).

Testicular atrophy was present in seven patients, and the testicles were absent in another (case 33), who had the physical characteristics of a eunuch. In two male patients there was no mention of the status of the testicles on physical examination.

HEMATOLOGIC OBSERVATIONS

Peripheral Blood: The criterion used for anemia was a red blood cell count under 4.0 million per cubic millimeter, for leukopenia a white blood

TABLE 4

Autopsy Findings on 14 Patients with Aplastic Anemia

Case No.	Grayish Brown Skin Pig.	Liver				Pancreas			Spleen		Lymph Nodes		Myocardium		Kidney	Testicular Atrophy	Bone Marrow			Duration of Illness	Number of Transfusions	Exogenous Hemochromatosis
		Size in Gm.	Hemosiderin		Portal Fibrosis	Hemosiderin		Fibrosis	Size in Gm.	Hemosiderin	Enlarged	Hemosiderin	Hemosiderin	Lipofuscin	Tubular Epith.		Hemosiderin	Cellularity				
			R-E	Epith.		R-E	Epith.											Axial	Femur			
21	Negro	2,600	2	1	1	3	2	2	220	3	No	1	0	2	1	Yes	2	H		1 yr. 10 mo.	96	Yes
24	No	1,500	0	0	0	0	0	0	150	1	Yes	2	0	0	0	Female	0	A	P	3 yrs.	41	No
25	Yes	2,250	2	3	1	2	3	2	365	2	No	3	0	2	1	Yes	1	myelocytic leuk.	P	1 yr. 6 mo.	103	Yes
28	Yes	2,400	2	3	1	3	2	1	360	3	No	3	0	2	1	Female	1	P***		12 yrs.	102	Yes
29	No	790	0	0	0	0	0	0	70	2	Yes	1	0	0	0	Female	3	A	H	1¼ mo.	5	No
30	No	3,200	0	0	0	0	0	0	600	1	Yes	1	0	0	0	No	2	A	H	2 mo.	17	No
32	Yes*	2,000	3	2	3**	3	3	0	475	3	No	3	2	3	1	Yes	3		P	14 yrs. 3 mo.	397	Yes††
33	Yes*	2,560	2	0	0	1	0	0	210	3	No	3	0	1	1	Yes†	1		P	20 yrs.	66	No
35	No	1,230	0	0	0	0	0	0	120	1	No	1	0	1	0	Female	0	H	P	2 yrs.	10	No
39	Yes	1,700	3	3	2	1	1	1	170	3	No		0	1	0	Female				2 yrs. 4 mo.	33	Yes
45	Yes	1,540	3	2	1	3	1	1	120	2	No	3	0	2	2	Female	3	P***	P	8 yrs. 3 mo.	71	Yes
46	No	1,730	1	1	0	0	0	0	270	2	Yes	1	0	0	3	No	2	A	A	7 mo.	19	No
49	No		0	0	0	0	0	0	150	0	No	0	0	0	0	No	1	A		3 yrs. 3 mo.	3	No
50	No	1,820	0	0	0	0	0	0	770	0	Yes	0	0	0	0	No	0	A	A	5 wks.	9	No

Key: 0-none, 1-slight, 2-moderate, 3-marked. A-markedly hypocellular, H-moderately hypocellular, P-slightly hypercellular.

* Hemosiderin present in the sweat glands.

** Advanced portal cirrhosis.

*** Erythroid hypoplasia.

† Testicles absent.

†† Although this patient had the most advanced degree of portal fibrosis, there was no fibrosis of the pancreas.

cell count under 5,000 per cubic millimeter, and for thrombocytopenia a platelet count under 100,000 per cubic millimeter by the indirect method. By these criteria, 37 patients presented with pancytopenia, seven with anemia alone, four with anemia and leukopenia, and two with anemia and thrombocytopenia. One patient (case 1) who presented with pancytopenia had only anemia following splenectomy. Another (case 25) presented with anemia and leukopenia, later developed pancytopenia, and died with acute leukemia with an elevated white count.

Thirty-two patients had a macrocytic anemia (MCV greater than 93 cubic microns), and in 10 patients the anemia was normocytic (MCV 81 to 93 cubic microns). None had a microcytic anemia (MCV less than 81 cubic microns). There were insufficient data to calculate the MCV in eight patients. In seven patients the anemia was quite macrocytic, with an MCV greater than 115 cubic microns, and in 24 patients it was greater than 100 cubic microns. Table 5 shows the type of blood cell depression and type of anemia encountered.

TABLE 5

Hematologic Observations in 50 Patients with Aplastic Anemia

Type of Anemia	MCV in Cu. μ	No.	Presenting Type of Peripheral Blood	No.
Macrocytic	>93	32	Anemia alone	7
Normocytic	81 to 93	10	Anemia, leukopenia	4
Microcytic	<81	0	Anemia, thrombocytopenia	2
Insufficient data		8	Pancytopenia	37

Forty-three of the 50 patients had an increased percentage of lymphocytes (over 40%) in their peripheral blood. There was a relative lymphocytosis in 37 and an absolute increase in lymphocytes (over 3,000 per cubic millimeter) in six. It is noteworthy that, of the seven patients with a normal percentage of lymphocytes in their differentials, four were patients with anemia alone. It is also of interest that, although 41 patients had leukopenia, only five had an absolute decrease in lymphocytes (less than 1,500 per cubic millimeter), indicating that lymphocyte production was not depressed in most of these patients.

One patient (case 13) showed nucleated red blood cells in the peripheral blood amounting to one to two nucleated red blood cells per 100 white blood cells counted. Two patients were found to have myelocytes in the peripheral blood. One (case 20) had 3% myelocytes on one occasion, and the other (case 25) had myelocytes in the peripheral blood when he developed acute leukemia terminally.

It was not uncommon in this series of patients to have an increased percentage of reticulocytes. There were 11 patients with reticulocyte counts greater than 5%, 10 with counts ranging from 2% to 5%, and 29 with

counts below 2%. Only nine patients had reticulocyte counts that were consistently 0.1% or less.

Bone Marrow: Bone marrow aspiration was performed on every patient, and in cases where the marrow was hypocellular repeated aspirations from various sites were carried out in all but a few instances. The findings on aspirated samples correlated well with the findings at autopsy and with the three surgical biopsies obtained, in all but two patients.* All of the specimens showed normoblastic erythropoiesis, and none showed tumor cells or myeloma cells. The only data tabulated from the whole group concern the type of cellularity found and the percentage of lymphocytes present, since these two features were recorded most consistently during the years covered by this study.

TABLE 6

Presenting Type of Bone Marrow in 50 Patients with Aplastic Anemia

Presenting Type of Bone Marrow	No.	Comment
Hypercellular	5	One later became hypocellular (Case 28)
Normocellular	8	Two showed erythroid hypoplasia (Cases 32, 38) Three later became hypocellular (Cases 42, 46, 47)
Hypocellular	37	Three later became hypercellular (Cases 1, 3, 25) Three later became normocellular (Cases 4, 7, 12)

Table 6 shows the presenting type of bone marrow found in this study. Most of the patients (74%) presented with a hypocellular bone marrow, but three of these later became hypercellular; in one (case 1) a hemolytic element became more pronounced, another (case 3) had a spontaneous remission, and the third (case 25) developed acute leukemia. Three patients (cases 4, 7 and 12) whose bone marrows were hypocellular when first seen later had normocellular marrows after remissions. The cellularity of the bone marrow was normal in eight patients, but two of these (cases 32 and 38) showed erythroid hypoplasia, and three (cases 42, 46 and 47) later became hypocellular. Five patients presented with a hypercellular bone marrow, and one of these (case 28) later became hypocellular.

Differential counts on the bone marrow were available in 37 patients, and in 27 of these more than 20% of the cells were counted as lymphocytes. In 18 patients more than 50% of the bone marrow cells were counted as lymphocytes, and in one patient (case 22) the increase was as high as 94%. Many observers studying the bone marrow in aplastic anemia have noted an increase in small round cells with deeply staining nuclei which closely resemble lymphocytes. Opinions regarding the identity of these cells have

* In one patient (case 25), bone marrow aspirated from the sternum two weeks prior to death was hypocellular, although 95% of the cells were myeloblasts, and at autopsy the sternal marrow was quite hypercellular. Another patient (case 45) was found to have a hypocellular marrow on two occasions nine months prior to autopsy, at which time the sternal marrow showed increased cellularity due to myeloid hyperplasia accompanied by erythroid aplasia.

differed. Rhoads and Miller [14] felt that they could distinguish these cells from lymphocytes by supravital staining, and thought that they were similar to the primitive cells described by Sabin et al.,[27] which were considered to be antecedent even to the hemocytoblast. Later Bomford and Rhoads [8] amplified their views on these cells, stating that they believed them to be early cells of the erythroid series. Smith [28] called them hematogones, and also thought they were progenitors of the erythrocyte series. On the other hand, Jordan [29] thought that they were lymphocytes which had migrated from lymphoid organs, and that they could serve as red cell precursors under conditions of stress. Davidson et al.[22] called them "Q" cells, and thought they were pathologic myelocytes with arrested development of granules. The true nature of these cells is still in doubt, but the fact that they are found in increased numbers in the bone marrow of patients with aplastic anemia seems to be well established and is borne out in our series of patients.

Leukocyte Alkaline Phosphatase: Blood smears were stained for the presence of alkaline phosphatase activity according to the method described by Wiltshaw and Moloney,[30] and the activity of alkaline phosphatase present in the neutrophils quantitated on a 0 to 4 plus basis. Eight patients were available for this determination, and five of them had values below the normal range (20% to 40%). These patients (cases 1, 3, 5, 12 and 14) had 12%, 2%, 11%, 6%, and 5% of their neutrophils giving a positive stain for alkaline phosphatase, respectively. It is of interest that one patient (case 12) had a value of 6% prior to treatment with prednisone, and during a remission while on prednisone had a value of 39%. After prednisone was discontinued a hematologic relapse occurred and the alkaline phosphatase value fell to 7%. Valentine et al.[31] have reported an increase in leukocyte alkaline phosphatase activity following the administration of ACTH and cortisone to patients with previously normal values. One patient (case 4) with normal values of 21% and 30% had been in complete remission for three years following splenectomy. Two patients (cases 6 and 15) had elevated alkaline phosphatase levels of 85 and 90%, respectively. Case 6 had a hypercellular bone marrow and evidence of increased hemolysis. Case 15, whose bone marrow was hypocellular, had pneumonia at the time the blood smear was obtained, but the white count was only 2,300 per cubic millimeter, with 41% neutrophils. Of the positively staining cells, 24% were graded 3 plus and 64% were graded 4 plus.

Etiology

Heredity: The first evidence of a familial factor in aplastic anemia was reported in 1927 by Fanconi,[32] who described the occurrence of aplastic anemia associated with other developmental defects in three brothers. Since then many cases that fit this syndrome have been described. Dawson [33] reviewed all the cases reported up to 1955, mentioned the different types of congenital anomalies found, and pointed out that all the cases showed

scattered areas of brownish pigmentation of the skin. Reinhold et al.[34] reviewed this syndrome from a genetic point of view and concluded that the reported cases would fit the predicted incidence of a recessive trait. Estren and Dameshek [35] have reported the occurrence of familial hypoplastic anemia without other associated defects in three of seven siblings in one family and in five of 14 siblings in another family, both of French Canadian origin. In the series reported by Loeb et al.[25] there were two brothers with red cell aplasia, and Wallman [36] has reported red cell aplasia occurring in a father and daughter. Further evidence of a possible hereditary factor was cited by Huber,[37] who studied the relatives of three patients who died of idiopathic aplastic anemia. He found that six of 23, four of 16, and three of 18 relatives, respectively, showed a slight neutropenia and anemia, while none of the 11 relatives of a patient with aplastic anemia due to trichloroethylene showed any hematologic abnormalities.

In the present series nine patients gave a positive family history for anemia, but only the two brothers with Fanconi's syndrome (cases 10 and 49) were documented examples of the familial occurrences of aplastic anemia. The only hereditary defect that these brothers had other than anemia was scattered areas of brown skin pigmentation. Although there was no other family history of anemia, there was a history of similar brown pigmentation in two maternal uncles and a maternal second cousin. Another patient (case 43) had Fanconi's syndrome with congenital anomalies of the thumbs. This patient had no family history of anemia. Although his mother gave a history of frequent nose bleeds, she was not anemic at the birth of the patient and there were no further blood studies.

Table 2 gives the racial incidence of aplastic anemia in 196 patients. Of this number only 3% were Negroes. The patients making up these series came from the New York area,[6, 8, 17] St. Louis,[25] many different localities,[26] and Virginia. Our series was collected in a hospital where approximately 15% of the admissions are Negroes, and only two of the 50 patients were Negroes. In one of these Negroes (case 21) the anemia was thought to be due to exposure to benzene, while the other (case 26) had a sudden onset and course lasting only two and one-half months. Chronic idiopathic aplastic anemia was not observed in a Negro. It appears from the collected cases as well as from our own that there is a lesser incidence of this disease in Negroes. The occurrence of familial cases of aplastic anemia and the difference in incidence between the white and Negro race suggest that hereditary factors may play a role in the etiology of some cases of this disease. Perhaps a defect in the development of the bone marrow is transmitted which is manifested by inadequate blood production early in life, or as an increased susceptibility to various bone marrow toxins, exogenous or endogenous, later in life.

Exposure to Toxic Agents: A wide variety of drugs and chemical agents have been reported to cause aplastic anemia. These various agents have

been well reviewed and classified by Osgood,[38] Welch [39] and Wintrobe.[40] The most common offenders have been benzol and its derivatives,[41-44] organic arsenicals,[45] chloramphenicol,[39, 46, 47] Mesantoin,[48] gold preparations,[49] and antibiotics other than chloramphenicol.[39]

It is quite difficult in most cases to assess the etiologic importance of exposure to a potentially toxic substance. Often patients have been exposed to multiple drugs, any one of which might be incriminated as a bone marrow toxin. Even when there is a good history of exposure to a single toxic agent, there remains the possibility that the relationship between the anemia and the exposure is a fortuitous one. On the other hand, many patients who give no history of toxic exposure and are classified as idiopathic might well have had significant exposure which went undetected. Even though the history of exposure is of doubtful significance, when groups of patients with aplastic anemia are studied only a small percentage of the cases give a definite history of exposure to toxins. In our collected data (table 2) only 21% of 302 patients had a positive history for toxic exposure.

In our series seven of the 50 were thought to have anemia because of exposure to potentially toxic agents. Three patients (cases 16, 21 and 22) had a history of exposure to benzol or related substances. One patient was exposed to each of the following: case 8 to phenylbutazone used in treating rheumatoid arthritis, case 9 to Mesantoin used for treatment of grand mal epilepsy, case 29 to chloramphenicol used prophylactically to prevent tonsillitis, and case 30 to an arsenical fruit-tree spray. All of these agents are common offenders, as mentioned above, except phenylbutazone. Although phenylbutazone has been reported frequently to cause agranulocytosis,[50] it only rarely causes a significant pancytopenia,[51, 52] and to the best of our knowledge case 8 represents the only recorded example of a selective depression of erythropoiesis.* Moderate decreases in hemoglobin and hematocrit have been felt to be due to a dilution phenomenon,[53] but in this case the hematocrit fell from 42% to 22%, there was erythroid aplasia on bone marrow examination, and a reticulocytosis of 10.4% occurred when the drug was withdrawn and prednisone treatment instituted. No reticulocytes had been seen prior to starting prednisone.

In addition to the patients mentioned above, four patients (cases 3, 6, 22 and 42) gave a history of having taken multiple medications prior to the onset of their illness, but the nature and amounts of these drugs could not be accurately ascertained, so that no drug could be definitely suspected. Antihistamines have been reported to cause bone marrow depression,[37, 54] and case 22 had been taking Chlor-trimeton and Pyribenzamine along with several other unknown drugs for an upper respiratory infection, but the history was too vague to indict these agents in this case. Another patient (case 28) had received intravenous therapy for "arthritis" for a two-year

* Case 8 will be reported in detail by the Allergy Division of the University of Virginia School of Medicine.

period up to one year before the onset of her illness. This medication may well have been gold, but we were unable to confirm this suspicion.

Endocrine Factors: The only significant endocrinologic disturbance which occurred in our series of patients was hypogonadism in eight patients. Seven had testicular atrophy, and in one (case 33) the testicles were absent. Autopsy was performed on four of these patients and confirmed the testicular atrophy in three (cases 21, 25 and 32) and the absence of testicles in case 33 (table 4).

It has been pointed out previously that eunuchs have a reduced red blood cell count which may be increased by androgen administration,[55, 56] and Watkinson et al.[57] have reported two cases of hypopituitarism and hypogonadism whose anemia improved following testosterone therapy. Partial remissions have been reported [58, 59] in patients with myelofibrosis treated with testosterone. Kennedy and Gilbertsen [60] have reviewed the effects of androgens on erythropoiesis, and pointed out the increase in red blood cell count often found in women with breast cancer treated with androgenic hormones.

Of our eight patients with hypogonadism, three received testosterone therapy with essentially no change in their blood picture. Case 33 received testosterone for a period of 12 years,* with an increase in his strength, appetite and weight. Although there was a slight rise in his blood cell values after taking testosterone for two months, the significance of this is uncertain. Cases 13 and 32 failed to respond to testosterone, but later in their course both of these patients responded to corticosteroid therapy. Case 13 had a complete remission after prednisone therapy, and case 32 had a partial remission after cortisone (which will be reported in detail). Case 10, who had Fanconi's syndrome, was treated with testosterone with no response. It is of interest that testicular atrophy has been noted in hemochromatosis and in animals who were overloaded with iron.[61, 62] Our three patients who had testicular atrophy confirmed at autopsy had each received multiple transfusions and were found to have excessive amounts of hemosiderin in their tissues. The onset of testicular atrophy could not be determined in these patients.

Liver Disease: Bomford and Rhoads [8] and Barker [63] reported that many of the patients with aplastic anemia that they studied showed evidence of liver disease. The former hypothesized that liver dysfunction might be an important factor in the etiology of this disease as a result of a failure in its usual biochemical mechanisms of detoxification. Both of these authors used the bilirubin excretion test, the sodium benzoate conversion test, and the measurement of urobilinogen in the urine and feces as measures of liver function. Bomford and Rhoads [8] found one or more of these tests to be abnormal in 14 of 26 patients, and Barker [63] found evidence of impaired

* Therapy consisted of intramuscular injections of 25 mg. of testosterone propionate twice weekly for 15 months, and then 10 mg. of methyltestosterone three times daily orally for the remaining time.

liver function in eight of the 16 patients that he studied.* On the other hand, Adams,[24] who reviewed 27 cases of aplastic anemia, stated that no evidence of liver disease was found when the serum bilirubin, serum alkaline phosphatase, total plasma protein and albumin/globulin ratio were used as tests of liver function.

The results of various liver function tests obtained in our study were as follows: Three of 11 patients had bromsulfalein retention greater than 5% after 45 minutes, six of 25 had an elevation of their prothrombin time of more than 2 seconds above the normal control, five of 21 had a serum bilirubin greater than 1.5 mg.%, six of 25 had a total serum protein below 6.0 gm.%, none had a reversal of the albumin/globulin ratio, eight of 14 had a cephalin flocculation of more than 2 plus after 48 hours, five of 18 had a thymol turbidity of more than 6.0 units, and two of nine had an alkaline phosphatase of greater than 4.0 Bodansky units. Twenty-five patients had a combination of at least three of the above mentioned tests and were felt to have sufficient data to estimate their liver function, and only six of these showed definite abnormalities. Three of these patients (cases 21, 32 and 39) were found to have exogenous hemochromatosis at autopsy (table 4), and the other three (cases 4, 33 and 48) had received multiple transfusions and had brownish gray pigmentation of the skin with hepatomegaly. It is difficult, if not impossible, to determine whether the anemia or the liver disease came first in these patients, but it is noteworthy that in three (cases 4, 21 and 32) the liver functions were normal early in the course of their illness and became abnormal as the duration of their disease and the number of transfusions increased. This problem of the relationship of liver disease to iron overload will be discussed in more detail in the section dealing with exogenous hemochromatosis.

Exogenous Hemochromatosis

The term "exogenous hemochromatosis" was introduced by Schwartz and Blumenthal [64] in 1948 to describe those patients who had received large amounts of exogenous iron, mainly by multiple transfusions, and at autopsy had diffuse fibrosis of the liver and pancreas in addition to abnormal amounts of hemosiderin in the tissues. At that time they could find only 13 patients, included five of their own, who fit this description, but when Schwartz [65] reviewed the problem again in 1956 he found that approximately 80 such cases had been reported. These have varied from mild cases, with only a small amount of fibrosis of the liver and pancreas, to advanced cases, with all the clinical features of idiopathic hemochromatosis.

Although the great majority of these cases have followed multiple transfusions, the condition has been reported to occur in patients who have been anemic for a long period of time and have received few or no transfusions.[66–70]

* Some of the same patients were studied by Bomford and Rhoads [8] and Barker [63] and were included in both studies.

It has been pointed out by Finch et al.[71] that in anemia characterized by a decrease in blood production and iron utilization there is a shift of iron to the storage depots. Furthermore, Dubach et al.[72] have shown that patients with this type of anemia absorb more iron than they use for hemoglobin. This is a possible explanation for the observation that patients with exogenous hemochromatosis have sometimes been reported to have more iron in their tissues than can be accounted for by the transfusions they received.[73-75] Thus, it would appear that patients with aplastic anemia may have their tissues overloaded with iron not only from transfusions but also as a result of the continued absorption of iron which they are unable to utilize.[25, 71] This is aggravated by the administration of the medicinal iron which most of these patients receive during the course of their illness.

TABLE 7

Serum Iron and Iron Binding Protein Values on 16 Patients With Aplastic Anemia

Case No.	Type of Bone Marrow When Specimen Was Obtained	Duration of Disease When Specimen Was Obtained	No. of Transfusions When Specimen Was Obtained	Oral Iron Therapy	Serum Iron Microgm. %	Unsaturated Iron Binding Protein Microgm. %
2	hypocellular	2½ mo.	12	Yes	166	Saturated
3	normocellular	1 yr. 4 mo.	0	No	137	270
4	hypocellular	6 yrs.	128	Yes	256	Saturated
5	hypercellular	17 yrs. 4 mo.	4	Yes	193	Saturated
6	hypercellular	3 yrs. 9 mo.	8	Yes	100	270
8	hypocellular	2 weeks	0	No	260	Saturated
9	hypocellular	1 mo.	0	No	225	Saturated
10	hypocellular	3 yrs. 10 mo.	7	Yes	276	Saturated
12	hypocellular	1½ mo.	0	No	127	187
	hypocellular	1 yr. 3 mo.	24	Yes	241	Saturated
13	hypocellular	2 yr. 3 mo.	32	No	252	—
15	hypocellular	1 yr. 3 mo.	4	Yes	98	180
19	hypocellular	6 yrs.	51	Yes	253	—
21	hypocellular	9 mo.	31	Yes	168	90
25	hypocellular	4 yrs.	93	Yes	230	Saturated
30	hypocellular	1 mo.	9	No	166	Saturated
32	normocellular	14 yrs.	397	Yes	142	Saturated

Serum Iron and Iron-Binding Protein Determinations: The serum iron level has been found to be elevated [19, 25, 40] and the iron-binding protein saturated [25] in most patients with aplastic anemia, and this was the case in our series. The serum iron level was determined in 16 of our patients and was elevated (above 150 μg.%) in 12, the level being above 200 μg.% in eight of these. The iron-binding protein was measured in 14 patients and was completely saturated in 10, below the normal of our laboratory (200 μg.%) in two, and normal in two. In table 7 these values are correlated with the type of bone marrow, number of transfusions, and duration of illness at the time the specimen was obtained. It is interesting that two patients (cases 8 and 9) thought to have anemia for only two weeks and one month, respectively, who had received no oral iron or transfusions, both had elevated serum irons and saturated iron-binding proteins. Another

patient (case 12) had a normal serum iron and unsaturated iron-binding protein when he was first seen, approximately six weeks after the onset of symptoms and before receiving any transfusions or oral iron therapy. When these values were checked again about a year later, the patient having received 24 transfusions and medicinal iron in the interim, the serum iron was 241 μg.% and the iron-binding protein was saturated. Case 4 is also of interest in that the serum iron was 256 μg.% and the iron-binding protein saturated in 1954, at which time the patient had been anemic for six years and had received 128 transfusions. The patient then had a complete remission following splenectomy, and three years later, although the blood counts and bone marrow had remained normal, the serum iron was still elevated (252 μg.%) and the iron-binding protein still saturated. This is in contradistinction to the experimental observations reported by Brown et al.,[62] who overloaded dogs with iron and found that the serum iron and iron-binding protein returned to normal approximately six months after the administration of iron was stopped in spite of massive amounts of iron in the tissue stores. However, the experimental dogs showed no evidence of impaired liver function, whereas our patient showed 15% bromsulfalein retention in 1954 and 20% retention in 1957. This emphasizes the importance of the liver in regulating the serum iron.

Autopsy Findings: Autopsies were performed on 14 patients, and six of these showed exogenous hemochromatosis. The criteria used in making this diagnosis were as follows: (1) abnormal amounts of hemosiderin in the tissues, (2) the presence of hemosiderin in the epithelial cells of the liver and pancreas as well as in the reticuloendothelial cells, (3) portal fibrosis of the liver, and (4) fibrosis of the pancreas. Dubin [76] has suggested that the term "hemochromatosis" be reserved for those patients with true cirrhosis with definite pseudolobulation and not just portal fibrosis. Only one of our patients (case 32) showed true cirrhosis by this definition, but we believe that the use of the term "hemochromatosis" may be justified, because several of the patients with only moderate portal fibrosis and no "true cirrhosis" had altered liver function which would not be implied by the term "hemosiderosis." Table 4 gives the autopsy findings with special reference to the problem of hemochromatosis. All of the cases were reviewed by Dr. David E. Smith, of the Department of Pathology, who graded the amount of hemosiderin found in the tissues and the amount of fibrosis found in the liver and pancreas.

When the autopsy findings were correlated with the number of transfusions received, it was found that all patients who had had more than 50 transfusions showed the changes of exogenous hemochromatosis except case 33, who had had 66 transfusions over a 20-year period. No patient who had received fewer than 50 transfusions had exogenous hemochromatosis except one (case 39), who had received 33 transfusions over a period of 28 months. In case 24, who had received 41 transfusions over a three-

year period (an amount similar to that received by case 39), exogenous hemochromatosis did not develop. However, case 24 had menorrhagia throughout her course, whereas case 39 was postmenopausal during her illness. Five of the six patients who showed exogenous hemochromatosis at autopsy had had liver function tests, and these were abnormal in three (cases 21, 32 and 39). Four had had blood sugar determinations, and these were elevated in two (case 21 and 28), but neither had had glycosuria. Although additional patients had features suggestive of exogenous hemochromatosis, such as brownish gray pigmentation of the skin, an enlarged liver and abnormal liver function tests, they are not included in this discussion since no autopsy data were available on these patients.

There seems to be little doubt that a recognizable entity, consisting of excessive amounts of hemosiderin in the tissues, accompanied by fibrosis of the liver and pancreas, occurs in a significant number of patients with long-standing anemia, most of whom have received multiple transfusions. This entity (exogenous hemochromatosis) and idiopathic hemochromatosis are both characterized by the accumulation of excessive amounts of iron in the tissues, and are distinguished from hemosiderosis by the presence of tissue damage. We agree with Finch [77] that the main difference between the exogenous form and the idiopathic form is the mechanism by which this excess iron is accumulated: by means of blood transfusions and excessive iron intake in the former, and by means of a congenital absorptive abnormality in the latter. There is much controversy as to whether these large deposits of iron actually cause the fibrosis which is found. Schwartz [64, 65] and Finch [71, 77] feel that excessive amounts of iron cause tissue fibrosis, whereas Rather [61] has summarized the various reasons for not accepting this view. The main evidence against iron per se as a cause of the fibrosis is the fact that the many animal experiments attempting to produce fibrosis in this way have been uniformly unsuccessful. Brown et al.[62] have recently reviewed these experiments and added similar data of their own. However, the one feature that all of the human cases have in common—and that was present in none of the animal experiments—is anemia. Such prolonged anemia, with resultant hypoxia or other derangement of cellular metabolism, might render tissues such as the liver and pancreas susceptible to a potential toxic effect of iron. The incidence of exogenous hemochromatosis in our cases seems to correlate well with the duration of the disease and the number of transfusions given, and supports the concept that if enough iron is given over a long enough period of time to a patient with aplastic anemia there is a significant risk of producing fibrosis and functional damage to the liver and pancreas.

Hemolytic Component

Bomford and Rhoads [8] studied 30 of their series of patients for evidence of increased blood destruction by measuring the fecal urobilinogen, and

found this to be abnormally high in 15 of these patients. They pointed out that an even greater number of patients might have shown evidence of hemolysis if calculations had been made to correct for the markedly reduced hemoglobin level in most of these patients (hemolytic index). Barker,[63] studying some of the same patients, found an elevated fecal urobilinogen excretion in eight of 25 patients. Loeb et al.[25] studied 10 patients with chronic bone marrow failure for hyperhemolysis by means of the fecal urobilinogen excretion, hemolytic index and red cell survival time, and found evidence for a hemolytic component in six of the 10. On the other hand, Spaet et al.[9] found no evidence of hemolysis in 19 patients with aplastic anemia as judged by the fecal urobilinogen and the hemolytic index.

Crosby [78] has recently reviewed 57 cases of auto-immune hemolytic anemia and has pointed out that decreased reticulocytes, leukocytes and platelets are a not uncommon finding in this disorder, and others [79-84] have suggested that auto-immunization may be the cause of some cases of idiopathic pancytopenia. Wasserman [85] has used the term "hemopathic hemolytic anemia" for those cases associated with various conditions in which there is decreased blood production by the bone marrow as well as decreased survival of the cells, and has pointed out that in many of these cases the hemolysis is slight and could easily be compensated by normal bone marrow function.

Many of the patients in our series showed evidence of a hemolytic element to their anemia, but they also showed decreased blood production, which was thought to be the main defect. Fourteen patients were studied with four-day fecal urobilinogen determinations, and the hemolytic index was calculated as described by Miller et al.[86] While only three patients had an elevated fecal urobilinogen level (above 200 mg./day), eight had an elevated hemolytic index (above 21). It should be pointed out that this group is probably biased, since patients suspected of having increased hemolysis were more likely to be studied with this test. One patient's fecal urobilinogen excretion (case 4) returned to normal following splenectomy, and another's excretion (case 1) was less after splenectomy, but the hemolytic element has continued and is now the most prominent aspect of the anemia. However, the patient had been anemic for approximately two years before she showed evidence of increased hemolysis.

Relationship to Leukemia

Although various illnesses may be confused with aplastic anemia, aleukemic leukemia presents the most difficult problem in differential diagnosis. Both of these conditions may present with pancytopenia, a hypocellular bone marrow aspiration and a few early white cells in the peripheral blood. Only the passage of time reveals which of these two disorders is present. It is uncertain whether these are two separate disorders with a similar clinical picture, or whether aplastic anemia may represent an early stage of

leukemia. Adams [24] felt that they were different phases of the same illness, and cited one of his 27 cases who terminally developed leukemia after a nine-month illness. Meacham and Weisberger [87] reported the early manifestations of six patients who subsequently developed leukemia. Five of these patients presented with pancytopenia, and one patient went 34 months before the diagnosis of leukemia became evident. The bone marrow was hypercellular in all of these patients. Block et al.[88] described the preleukemic phase of acute leukemia in 12 patients. Six of these had features suggesting aplastic anemia, and one was followed for 17 months before the diagnosis of acute leukemia became apparent. The bone marrow was hypocellular in three and hypercellular in the other three. It is noteworthy that cases of benzol poisoning have run the gamut from an aplastic anemia picture to leukemia, and that exposure to this one agent may lead to both of these diseases.[41, 43, 89, 90] Another observation which tends to link these two diseases is the occurrence of Fanconi's syndrome and leukemia in the same family, one example occurring in two brothers and another example in cousins.[91] Also, the incidence of leukemia is lower among American Negroes than among whites,[92] which was also true of the incidence of aplastic anemia in this study. However, the great majority of cases of aplastic anemia do not pass over into leukemia, and these two conditions can usually be differentiated early in their course by examining the bone marrow and by the fact that patients with aleukemic leukemia are more likely to have prominent lymphadenopathy and splenomegaly.

No patients were excluded from our series because they developed leukemia as long as the original diagnosis was thought to be aplastic anemia. Thirty-eight of our cases were followed for over a year, and only one (case 25) developed leukemia. This patient's course lasted four and one-half years, and he developed acute leukemia during the last six weeks of his life. He will be reported in detail. Another patient (case 50) was thought to have aleukemic leukemia clinically because of generalized lymphadenopathy, splenomegaly, and an increased number of early white cells in the bone marrow, but at autopsy was found to have aplastic anemia. This case will also be reported in detail.

Prognosis

The prognosis in aplastic anemia was formerly thought to be very poor, with few patients surviving more than a year and remissions a rarity. When Smith [20] reviewed the literature in 1919 and collected 62 cases, only three had survived more than a year and only one had had a remission. In more recent years it has become apparent that many of these patients survive for prolonged periods and that remissions are not uncommon. Thus, in Bomford and Rhoads's [8] series of 66 cases, 15 recovered completely. Thirteen of these had been exposed to potential toxins, and they felt that the recoveries were spontaneous and not related to any form of therapy

other than the removal of the suspected toxin. In Boon and Walton's [23] series of 25 cases, six of whom had been exposed to toxins, nine had complete remissions. Tsai [26] has recently reviewed 26 cases of erythrocytic hypoplasia, 11 of whom recovered completely. Two of these remissions were spontaneous, and the other nine were thought to be due to various forms of therapy. Only two of the patients had a history of toxic exposure.

Duration of Illness: Table 8 shows the duration of illness in our series of patients correlated with the presenting type of peripheral blood. The duration of illness of the 15 patients still living varies from 15 months to 17½ years. Nine patients have had their illness from one to three years, three for more than five years, and one for more than 10 years (case 5). The duration of illness of the 35 patients who have died varied from five weeks (case 50) to 20 years (case 33). Twelve patients lived less than a year from the onset of their illness, while 15 survived more than three

TABLE 8

Survival in 50 Patients with Aplastic Anemia

Presenting Type of Peripheral Blood	No. of Pts.	Alive Years Survival				No. of Pts.	Dead Years Survival			
		1	3	5	10		1	3	5	10
Anemia	4	4	2	2	1	3	3	3	2	1
Anemia, leukopenia	0					4	4	3		
Anemia, thrombocytopenia	0					2	2	1	1	1
Pancytopenia	11	11	7	1		26	14	8	5	2
Total	15	15	9	3	1	35	23	15	8	4

years, eight more than five years, and four more than 10 years. Patients with anemia alone had the most favorable prognosis, patients with pancytopenia the worst. All seven patients with anemia alone survived for more than a year, five for more than three years, four for more than five years, and two for more than 10 years. All of the 12 patients who died in less than a year had pancytopenia, but it is important to note that six of the 37 patients who presented with pancytopenia lived longer than five years. Patients who presented with a hypercellular bone marrow had a better prognosis than did those with a normocellular or hypocellular one, but there was no statistical difference in the prognosis of patients who presented with the latter two types. All five patients with a hypercellular bone marrow were alive after one year, four after three years, and two after 10 years.

Remission: Six patients recovered from their aplastic anemia with return of blood values to normal. All of these patients are still living, with remissions lasting from two months to three years. Four patients (cases 7, 8, 9 and 13) had remissions after corticosteroid treatment, but two of these (cases 8 and 9), whose anemia was thought to be due to exposure to phenylbutazone and Mesantoin, might well have had a remission without

steroid therapy as a result of the withdrawal of the suspected agent. The two others (cases 7 and 13) have been in complete remission for more than a year. One patient (case 4) had a remission after splenectomy, and another (case 3) had a spontaneous remission. The presenting type of bone marrow was hypocellular in all of the patients who had complete remissions. Two of the patients (cases 4 and 8) had anemia alone, while the other four had pancytopenia. Only cases 8 and 9 had a history of toxic exposure.

Six patients had a partial or temporary remission. Two patients (cases 19 and 28) had spontaneous remissions lasting four and 8 years, respectively, but relapsed and died of their disease. Case 12 had a return of blood values to normal after treatment with prednisone but had a relapse when this

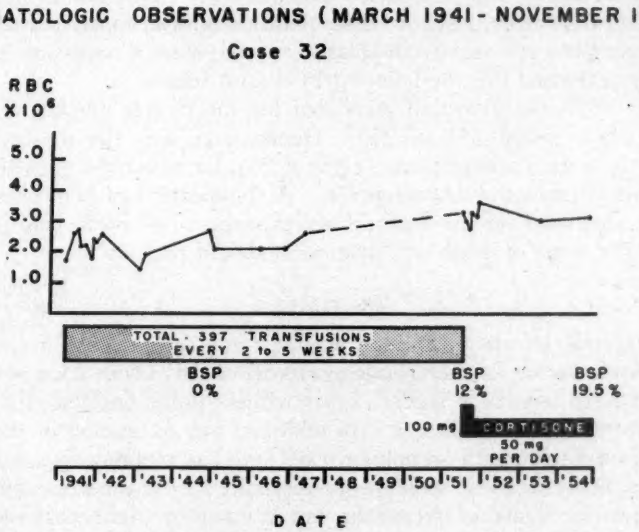

FIG. 1. *Case 32.* Hematologic observations (March, 1941–November, 1954).

drug was discontinued. Treatment was reinstituted, but there was no response after three months of therapy. Case 32, after having been anemic for 11 years, during which time he received 397 transfusions, was then treated with cortisone and, although his red cell values never returned to normal levels, he no longer needed transfusions and returned to a normal life. This partial remission lasted three years and four months before he died suddenly of pneumonia with no essential change in his blood picture (figure 1). Case 33, after having had pancytopenia for three years and having received 21 transfusions, went 17 years without transfusions and led an active life although there was only slight improvement in his blood values; he then developed severe pancytopenia and died of his disease in five months in spite of receiving 44 transfusions. Case 36 had a remission

with return of blood values to normal that lasted two years after receiving crude liver extract orally and intramuscularly. At the end of this time anemia recurred and failed to respond to liver in any form, and the patient died four years later of his disease. Four of these six patients had a hypocellular bone marrow, one (case 28) had a hypercellular marrow, and another (case 32) had a normocellular one. Three of the patients had pancytopenia, two (cases 12 and 32) had only anemia, and another (case 28) had anemia and thrombocytopenia. These figures indicate that patients with anemia alone are more likely to have a remission, since four of the seven patients with anemia alone had either a partial or complete remission, whereas this occurred in only seven of the 37 patients with pancytopenia. Cases 28, 32 and 33 will be reported in detail.

It is apparent from the above cases that it is difficult to say that a patient has had complete recovery from aplastic anemia, since a remission may last for many years and then be followed by a fatal relapse.

Cause of Death: Infection accounted for the largest number of deaths for the whole group (11 of 25). Hemorrhage was the most common cause in those with pancytopenia (eight of 26), but was not a cause of death in patients without thrombocytopenia. A combination of hemorrhage and infection accounted for the death of six patients, all of whom had pancytopenia. The cause of death was unknown in eight patients.

Treatment

Therapeutic efforts in aplastic anemia have been mainly unsuccessful, and the wide variety of therapeutic agents which have been tried, with only a few scattered reports of success, bears witness to the unsatisfactory status of the treatment of this disease. In addition, any evaluation of therapy is difficult in a disease with an unknown etiology and a clinical course characterized by fairly frequent spontaneous remissions. At the present time the most effective forms of treatment are transfusions, corticosteroids and splenectomy. It is of the utmost importance to try to elicit a history of toxic exposure and to eliminate any suspected toxin. Vitamin preparations such as B_{12} and folic acid have not been effective in this type of anemia, and iron therapy is not only useless but may also be harmful, as is pointed out in the section on exogenous hemochromatosis.

Transfusions: Most patients with aplastic anemia require repeated transfusions and because of the danger of transfusion reaction, serum hepatitis, and iron-overload inherent in this form of therapy, an effort was made to keep the number to the minimum compatible with the comfort of the patient. Many of these patients tolerated low levels of hemoglobin quite well, and no attempt was made to raise their counts to normal levels, as this may further depress the erythroid activity of the bone marrow.[93]

Corticosteroids: When ACTH and corticosteroids were shown to have a myelostimulatory effect,[94-96] it was suggested that they might be helpful

in the treatment of aplastic anemia.[97] These drugs are now used frequently in this disease, and several authors have reported improvement or remissions in a few patients.[9, 25, 98, 99] Loeb et al.,[25] using Fe^{59} utilization studies, found an increase in erythropoiesis after ACTH or cortisone therapy in all nine of the patients with bone marrow failure so studied. Five of these nine patients had isolated depression of erythropoiesis.

In our series, 34 patients were treated with corticosteroids in the form of either cortisone or prednisone. Six patients had a complete or partial remission, nine showed improvement in some feature of their illness, and 19 showed no response. Table 9 shows the response to treatment with corticosteroids correlated with the type of peripheral blood picture. It is interesting to note that, of the five patients with anemia alone treated with corticosteroids, three had remissions, whereas only three of the 29 patients

TABLE 9

Results of Corticosteroid Therapy in 34 Patients with Aplastic Anemia

Presenting Type of Peripheral Blood	No. of Pts.	Response		
		Remission	Improved	None
Anemia	5	3	0	2
Anemia, leukopenia	2	0	0	2
Anemia, thrombocytopenia	1	0	0	1
Pancytopenia	26	3	9	14
Total	34	6*	9	19

* 2 of these (Cases 8 and 9) were due to drugs (phenylbutazone and Mesantoin) and they might well have had a remission without the use of corticosteroids, and in one (Case 12) the remission was only temporary.

with other types of cells involved had a remission. The six patients (cases 7, 8, 9, 12, 13 and 32) who had a remission after corticosteroid therapy are discussed in the section on remissions, and case 32 will be reported in detail. Four of these patients (cases 7, 8, 9 and 13) recovered completely, one (case 12) had a temporary remission, and another (case 32) had a partial remission. No definite hematologic response was noted in two patients (cases 7 and 13) until after three months of therapy with cortisone. In one patient (case 8) there was a response in six days, and in another (case 12) in five weeks. In the other two patients (cases 9 and 32), the time of response could not be determined. Of the nine patients who showed some improvement, three (cases 22, 24 and 28) had a decrease in their bleeding tendency without a rise in platelet count, one (case 23) had a rise in platelet count, two (cases 1 and 3) had a rise in leukocyte count, and three (cases 10, 11 and 15) had a temporary rise in erythrocyte count.

Splenectomy: The role of splenectomy in aplastic anemia has been discussed recently by a number of workers in this field.[100–102] Moore [25, 100] feels that splenectomy should be performed only if there is evidence of a

hemolytic component or a response to corticosteroids, and Dameshek [9, 101] feels that this procedure is useless when the bone marrow is markedly hypocellular. On the other hand, Whitby,[101] Smith [102] and Kawakita [101] recommend splenectomy when other forms of therapy have failed. Splenectomy is performed in the hope of stopping the production of auto-antibodies, improving bone marrow function,[103, 104] and prolonging the survival of red cells when a hemolytic element is present. This procedure has been performed in a large number of patients with aplastic anemia and, although it

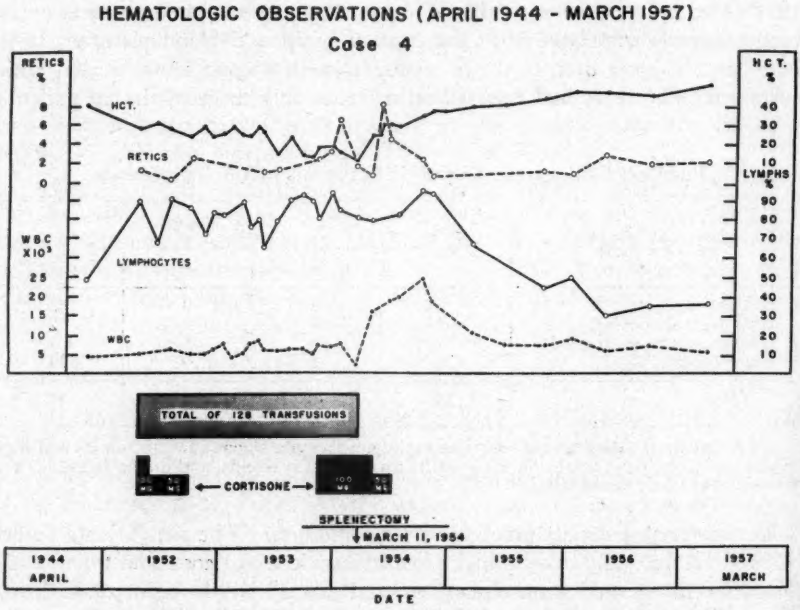

FIG. 2. *Case 4.* Hematologic observations (April, 1944–March, 1957).

has been effective in only a small percentage of cases, dramatic remissions have occurred.[9, 25, 26, 40, 101, 105, 106] In addition, some patients may respond better to corticosteroids after splenectomy.[25, 26]

In our series five patients had splenectomy. Case 4, who had been anemic for six years and had received 128 transfusions, had a complete remission following splenectomy and has been followed for three years with no signs of relapse. This patient had anemia with a hypocellular bone marrow, and developed evidence of increased hemolysis just prior to splenectomy. This case will be reported in detail (figure 2). Case 1 had a return of leukocyte and platelet count to normal levels but only a transient improvement in her anemia, which has a large hemolytic element. Case 14 had slight improvement in that transfusions were needed less frequently,

although there was no essential change in his red cell values. Cases 22 and 25 showed no response to splenectomy.

Illustrative Case Reports

Case 4. A white housewife had been in good health until 1944 when, at the age of 58, she developed chest pain and had a "nervous breakdown" which was associated with the complete loss of body hair. She was first seen at the University of Virginia Hospital on April 24, 1944, for chest pain. She had no evidence of heart disease, and blood studies revealed a hemoglobin of 11.5 gm.%, red cell count of 4.4 million per cu. mm., white cell count of 4,400 per cu. mm., with 2 bands, 44 neutrophils, 50 lymphocytes and 3 monocytes per 100 white cells. The platelets appeared plentiful on the blood smear. The patient was not seen again for eight years, when she was admitted to the hospital on April 18, 1952, because of weakness and chest pain. She had been found to be anemic by her local physician four years prior to admission, and had been treated by weekly injections of liver extract and had taken ferrous sulfate daily, with no response. She gave no history of exposure to toxic agents.

Physical examination revealed pallor and total absence of body hair. There was no superficial lymphadenopathy, but the liver and spleen were palpable just beneath the costal margins. No other abnormalities were noted.

Admission blood values were: hematocrit, 28%; hemoglobin, 8.5 gm.%; red cell count, 2.8 million per cu. mm., reticulocytes, 1.3%; white cell count, 5,000 per cu. mm., with 8 neutrophils, 90 lymphocytes and 2 monocytes per 100 white cells, and 194,500 platelets per cu. mm. Bone marrow aspirated from the sternum and iliac crest was hypocellular, contained 50% lymphocytes, and showed marked erythroid hypoplasia. Other studies included: fasting sugar, 112 mg.%; basal metabolic rate, plus 24, and free hydrochloric acid after histamine in the gastric aspiration.

Course: Figure 2 summarizes the hematologic course and treatment of this patient. She was treated with cortisone, liver extract, folic acid and ascorbic acid, with no response. During the remainder of 1952 and 1953 it was necessary to administer transfusions almost monthly, with progressively less benefit. In November, 1953, her status was reëvaluated, with the following findings: Her liver and spleen had gradually become larger; the liver was palpable 5 cm. below the right costal margin and the spleen 4 cm. below the left costal margin; hematocrit, 18%; hemoglobin, 5.7 gm.%; red cell count, 1.6 million per cu. mm., reticulocytes, 2.5%; white cell count, 7,000 per cu. mm., with 82% lymphocytes; platelets, 132,800 per cu. mm. A surgical bone marrow biopsy revealed a hypocellular specimen with marked reduction in both erythropoiesis and myelopoiesis, 50% of the cells being lymphocytes; serum iron, 247 μg.%; iron-binding protein, saturated; bromsulfalein, 2.5% retention in 45 minutes; thymol turbidity, 8.2 units; direct Coombs' test, positive. A four-day fecal urobilinogen determination averaged 219 mg. per day and gave a hemolytic index of 96 (normal, 11 to 21). It was apparent that there was a definite hemolytic component to this patient's anemia, and cortisone was started again, but with no benefit. She began having frequent febrile transfusion reactions in March, 1953, after receiving 40 transfusions, and was first noted to have a positive Coombs' test in November, 1953. In December, 1953, she had a moderately severe hemolytic transfusion reaction, and it was discovered that she was Kell-negative and had a high titer of anti-Kell in her serum, a finding which was thought to account for her positive Coombs' test and the decreasing benefit from transfusions. The remaining transfusions she received were with Kell-negative blood, and no reactions occurred. A splenectomy was performed on March 11, 1954. The spleen weighed 560 gm. and showed chronic congestive splenomegaly and hemosiderosis, but no evidence of ex-

tramedullary hematopoiesis or leukemia. After splenectomy she required no further transfusions, and her red cell values gradually returned to normal over a six-month period. Determination of the fecal urobilinogen was repeated seven months after splenectomy and had returned to normal. Cortisone was discontinued four months after splenectomy because of an episode of mental confusion thought to be a cortisone-induced psychosis. After splenectomy the white count remained elevated for several months, and the high percentage of lymphocytes in the peripheral blood, which had been present throughout her course, persisted for 18 months. She was last seen on March 28, 1957, three years after splenectomy, at the age of 71, at which time she was asymptomatic. Peripheral blood values were normal, and a bone marrow specimen which was normocellular contained only 11% lymphocytes. The only abnormalities detected were a liver palpable 4 cm. below the right costal margin, a bromsulfalein retention of 20% in 45 minutes, and a serum iron of 256 μg.% associated with a saturated iron-binding protein.

Comment: This patient had red cell aplasia associated with a high percentage of lymphocytes in the peripheral blood and bone marrow for about six years. The blood values gradually returned to normal following splenectomy. Her course was complicated by the development of a positive Coombs' test due to anti-Kell antibodies. She also developed hepatomegaly with abnormal liver function tests after receiving multiple transfusions.

Case 25. A white male plasterer was first found to be anemic in 1949, at the age of 65, and required transfusions every four to five months. He was first seen at the University of Virginia Hospital in September, 1952. The patient's father had died of "anemia." No history of exposure to toxic agents was elicited.

Physical examination was normal except for pallor. No enlargement of the liver, spleen or lymph nodes was detected.

Admission blood values were: hematocrit, 31%; hemoglobin, 10.4 gm.%; red cell count, 3.3 million per cu. mm.; reticulocytes, 0.5%; white cell count, 3,900 per cu. mm. with 60% neutrophils and 38% lymphocytes; platelet count, 200,000 per cu. mm.; osmotic fragility, normal except for incomplete hemolysis; fecal urobilinogen, 98 mg. daily; hemolytic index, 26; total bilirubin, 0.2 mg.%; Coombs' test, negative. Bone marrow aspirated from the sternum and iliac crest was markedly hypocellular and showed no evidence of leukemia. Barium study of the upper gastrointestinal tract was negative but revealed an enlarged spleen which could not be felt on physical examination.

Course: The patient was initially treated with cortisone and vitamin B_{12}, with no response, and on January 8, 1953, splenectomy was performed. The spleen weighed 365 gm. and showed congestive changes and marked hemosiderosis, but no evidence of myeloid metaplasia or leukemia. The patient did not improve following splenectomy, and needed transfusions almost monthly. In January, 1954, a brownish gray pigmentation of the skin was apparent, and the liver was palpable 2 cm. below the right costal margin. Liver function tests were normal. The serum iron was 230 μg.%, and the iron-binding protein was saturated. Fasting blood sugar was 128 mg.%. Treatment with hydrocortisone was started in March, 1954, and continued for three months, with no response. In April, 1954, the platelets were found for the first time to be reduced to 62,000 per cu. mm. On May 21, 1954, the white cell count was 1,600, and a myeloblast was seen in the peripheral blood for the first time. On June 18, 1954, the patient was admitted because of pneumonia. The white count was 6,000 per cu. mm. and 95% of the cells were myeloblasts. Bone marrow aspirated from the sternum was hypocellular, but almost all of the cells were myeloblasts, and many contained Auer's bodies. Chest x-rays showed

bilateral areas of consolidation, and blood cultures grew out Klebsiella and *Escherichia coli*. The patient ran a septic course, failed to respond to antibiotics, and died on July 4, 1954. During this final admission his white count gradually rose to 35,200, and he developed severe thrombocytopenia.

Autopsy Findings: At autopsy there was fatty replacement of the femoral bone marrow while marrow from the ribs, sternum and vertebrae was hypercellular. Practically all of the cells were myeloblasts, and no megakaryocytes were seen. This leukemic process also involved the lymph nodes and diaphragm, but not the liver. There was advanced generalized hemosiderosis involving the liver, pancreas, lymph nodes, epithelium of the stomach, renal tubules and thyroid, with fibrosis and atrophy of the pancreas, portal fibrosis of the liver and atrophy of the testes and thyroid (exogenous hemochromatosis—see table 4). There were generalized petechiae of the skin, epicardium, endocardium and kidneys. There was a bilateral organizing hemorrhagic pneumonia from which Klebsiellae were cultured, and a bilateral hydrothorax, hydropericardium and ascites.

Comment: This patient had aplastic anemia which failed to respond to corticosteroids and splenectomy. He received 103 transfusions, and at autopsy was found to have exogenous hemochromatosis. During the last six weeks of his illness he developed acute myelocytic leukemia. It seems unlikely that unrecognized leukemia existed from the onset of his illness, which lasted four and one-half years.

Case 28. A white housewife was first found to be anemic in 1940, at the age of 36, following the birth of her fourth child. She had excessive bleeding at the time of delivery, and menorrhagia when her periods started again. She gave a history of having had "arthritis" in 1937 and 1938, and had been treated by intermittent intravenous injections of an unknown medication. Because of excessive vaginal bleeding she had x-ray castration in 1940, and from 1940 to 1942 she received 53 transfusions. She had a spontaneous remission in 1942 which lasted eight years, during which time her hemoglobin varied from 75% to 80%. In 1950 she developed epistaxis, bleeding gums and purpura. She was again found to be anemic, received 37 transfusions, and was referred to the University of Virginia Hospital on January 8, 1952. There was no history of toxic exposure, with the possible exception of the intravenous injections mentioned above, which might have contained gold.

Physical examination revealed an obese white female (207 pounds), with pallor and purpura of the skin. There was bleeding from the gums and nose. There was no detectable lymphadenopathy, and the liver and spleen were not felt.

Admission blood values were: hematocrit, 30%; hemoglobin, 9.7 gm.%; red cell count, 3.2 million per cu. mm., reticulocytes, 0.1%; white cell count, 6,000 per cu. mm. with 46% neutrophils, 50% lymphocytes and 2% eosinophils; platelet count, 6,000 per cu. mm., tourniquet test, positive; bleeding time, 30 minutes; normal coagulation time; no clot retraction in 24 hours; fecal urobilinogen, 90 mg. daily; hemolytic index, 15; Coombs' test, negative. Bone marrow aspirated from the sternum was hypercellular because of increased myeloid activity, but erythropoiesis was normoblastic and not increased. Megakaryocytes were present in normal numbers. Additional laboratory studies included a fasting blood sugar of 132 mg.% and several LE preparations which were negative.

Course: The patient was treated with cortisone, ACTH and massive doses of vitamin B_{12}, with no response. She became markedly anemic, platelets disappeared from the blood smear, and her white count fell to 3,300. A bone marrow aspiration in February, 1952, showed myeloid hyperplasia with erythroid aplasia and only an occasional megakaryocyte. She continued to have epistaxis and bleeding from the

gums, received an additional 13 transfusions (total, 103), and died on June 7, 1952, of an intracranial hemorrhage.

Autopsy Findings: At autopsy the skin had a brownish tinge and there were multiple purpuric areas. The liver and spleen were enlarged, weighing 2,400 gm. and 360 gm., respectively. On microscopic examination there was marked hemosiderosis involving the liver, pancreas, spleen and lymph nodes, with fibrosis of the liver and pancreas (exogenous hemochromatosis—see table 4). The axial bone marrow showed slight myeloid hyperplasia and erythroid aplasia.

Comment: This patient had a spontaneous remission lasting eight years that was followed by a relapse which was fatal two and one-half years later. Her first period of anemia might have been related to intravenous gold, but this was never established. She was found to have exogenous hemochromatosis at autopsy.

Case 30. A 58 year old white sawmill worker was admitted to the University of Virginia Hospital July 12, 1955, with a three-week history of weakness, fever and anemia. Six weeks prior to admission he had mixed nine gallons of a fruit tree spray containing arsenic, lime and sulfur. He used all of this spray in about four hours without the protection of a mask.

Physical examination revealed marked pallor of the skin with no petechiae. There were bilateral retinal hemorrhages. The chest was emphysematous, and there was a grade II apical systolic murmur. The liver was felt 3 cm. below the costal margin, but the spleen was not felt.

Admission blood values were: hematocrit, 18%; hemoglobin, 5.0 gm.%; red cell count, 2.0 million per cu. mm.; reticulocyte count, 0.9%; white cell count, 3,600 per cu. mm. with 30% neutrophils, 65% lymphocytes and 5% monocytes; platelet count, 26,000 per cu. mm.; serum iron, 166 μg.%; prothrombin time, 15 seconds for the patient, 12 seconds for the control; cephalin flocculation, 3 plus in 48 hours; bromsulfalein retention, 2.4% in 45 minutes; Coombs' test, negative. Bone marrow aspiration revealed marked hypocellularity, and only a few cells which resembled reticuloendothelial cells were seen. Hair, nails and urine were negative for arsenic.

Course: This patient ran a septic course, and the white count dropped as low as 750 per cu. mm., with 3% neutrophils. He developed a Pseudomonas septicemia with pneumonia and a perianal abscess, and died on August 18, 1955, in spite of vigorous treatment with antibiotics, blood transfusions and cortisone.

Autopsy Findings: The skin showed several purpuric areas. The cervical, mediastinal and periaortic lymph nodes were enlarged. There was atelectasis of the right lung. The liver and spleen were enlarged, weighing 3,200 gm. and 600 gm., respectively. Microscopic examination showed multiple abscesses of the lungs and kidneys, and congestion of the spleen. Both the axial and femoral bone marrows were markedly hypocellular.

Comment: This patient had a rapidly fatal illness of eight weeks' duration, with marked agranulocytosis following exposure to an arsenical fruit-tree spray.

Case 32. A white farmer had been in good health until August, 1940, when, at the age of 54, he burned his legs with gasoline and was found to be markedly anemic. After treatment with liver injections and iron, without improvement, he was referred to the University of Virginia Hospital on March 6, 1941, with the chief complaints of weakness and exertional dyspnea. There was no family history of anemia and no definite history of toxic exposure, although he had used a spray of

unknown composition in his orchard for many years. He had had mumps during childhood which had "affected" his left testicle.

Physical examination revealed marked pallor of the skin and mucous membranes. There was minimal axillary lymphadenopathy, and the liver and spleen were felt two fingerbreadths below the costal margins. The left testicle was atrophied.

Admission blood values were: hematocrit, 19%; hemoglobin, 6.5 gm.%; red cell count, 1.5 million per cu. mm.; reticulocytes, 0.5%; white cell count, 7,800 per cu. mm., with 10% band forms, 56% segmented neutrophils, 32% lymphocytes, and 2% monocytes; platelet count, 506,800 per cu. mm. Bone marrow aspirated from the sternum was normocellular with erythroid hypoplasia. The urine was negative for arsenic and lead. Free hydrochloric acid was found on gastric analysis.

Course: Figure 1 shows the course of this patient's illness. From March, 1941, to July, 1951, the patient received many forms of therapy, including iron, liver extract, folic acid, thiamine, thyroid, and bone marrow transfusions by the direct method, all to no avail. During this time his red cell count varied from 1.7 million to 2.5 million per cu. mm. He required transfusions every two to five weeks, and received a total of 397 transfusions. He received his last transfusion on July 12, 1951, and was started on cortisone therapy July 16, 1951. After this he felt much stronger and needed no more transfusions. His red cell count stabilized at approximately 3.0 million per cu. mm.; hemoglobin, 10.0 gm.; hematocrit, 30%. During the course of his illness his liver and spleen became larger, he developed generalized lymphadenopathy, and his liver function tests became more abnormal. The bromsulfalein retention was 0% in December, 1944, 12% in July, 1951, and 19.5% in October, 1954. The serum iron was 172 μg.%, and the iron-binding protein was saturated in March, 1950. He never had glycosuria, and fasting blood sugar levels were normal. Throughout his course the white count and platelet count remained normal, repeated bone marrow aspirations showed no essential change, and the reticulocytes were never higher than 1.1%. The patient died suddenly at home on November 11, 1954, of a fulminating pneumonia after a prolonged period of anemia lasting 14 years, with a partial remission while taking cortisone during the last three years of his life.

Autopsy Findings: There was marked generalized hemosiderosis involving the liver, spleen, pancreas, lymph nodes, thyroid, testes, adrenal, pituitary, myocardium, endothelium of the blood vessels, gastric mucosa, glomeruli and tubular epithelium of the kidney, and sweat glands of the skin. The liver and spleen were enlarged and the liver was nodular, showing advanced cirrhosis on microscopic examination. The testes, pituitary, thyroid and adrenals were atrophic, and there was diffuse scarring of the mycardium. There was no fibrosis or atrophy of the pancreas (exogenous hemochromatosis—see table 4). The femoral bone marrow was somewhat hypercellular. There was generalized atherosclerosis involving the aorta and the coronary and renal arteries. The lungs showed extensive areas of lobular pneumonia.

Comment: This patient had a long-standing anemia (14 years), without involvement of the leukocytes or platelets, and had a partial remission after cortisone which lasted three years. He received 397 transfusions and was found to have exogenous hemochromatosis at autopsy.

Case 33. A white ice-carrier was first found to be anemic in 1933, at the age of 42, and was referred to the University of Virginia Hospital in March, 1933, when his anemia failed to respond to liver and iron therapy. At the time of admission he complained of marked weakness, purpura, epistaxis and bleeding gums. There was no family history of anemia, and no exposure to known toxins. He stated that he had never developed sexually.

Physical examination revealed a tall, thin male with wide hips, scanty body hair, female distribution of pubic hair, infantile penis and absent testicles. Ecchymoses of the skin and retinal hemorrhages were present. There was no detectable enlargement of the lymph nodes, liver or spleen.

Admission laboratory values were: hemoglobin, 40%; red cell count, 1.6 million per cu. mm; reticulocytes, 3.2%; white cell count, 2,600 per cu. mm., with 44% neutrophils, 52% lymphocytes, 4% monocytes and 1% eosinophils; platelet count, 12,800 per cu. mm.; osmotic fragility, normal. Free hydrochloric acid was found on gastric aspiration.

Course: In October, 1933, the patient was referred to the Rockefeller Institute in New York,* where the hematologic findings were similar to those listed above, and a bone marrow biopsy showed a "severely hypocellular marrow." From 1933 to 1936 the patient's red cell count ranged from 1.2 million to 2.4 million per cu. mm., and he received 21 transfusions. From April, 1936, to February, 1953, a period of 17 years, no transfusions were necessary, although there was no change in his blood values until October, 1941, when his red cell count increased slightly and stabilized between 2.6 million and 3.0 million per cu. mm. Testosterone therapy was instituted in August, 1941, and continued for the rest of his life. There was an increase in strength, weight and appetite, and a slight increase in the red cell count two months after beginning therapy. The patient did well, with only minor complaints, until April, 1953, when he was admitted to the Community Hospital at Gordonsville, Virginia, because of indolent necrotic ulcers on both lower legs. At that time the only change noted on physical examination other than the ulcerations was grayish brown pigmentation of the skin. He developed severe thrombocytopenia, accompanied by bleeding into the skin and gastrointestinal tract. Cortisone therapy was begun in May, 1953, with temporary improvement in his bleeding difficulties, but he gradually became worse in spite of multiple transfusions, and died July 13, 1953.

Autopsy: There were extensive petechiae and hemorrhages in the skin, spleen, lungs, thyroid and intestines, with the latter containing about 800 ml. of fresh blood. There was hemosiderosis involving the liver, spleen, pancreas, lymph nodes, and sweat glands of the skin. The liver and spleen were enlarged, and the liver showed focal areas of fibrosis but no portal fibrosis. There was no fibrosis of the pancreas, and no hemosiderin in the epithelial cells of the liver and pancreas. The femoral bone marrow showed atrophy, and the axial bone marrow was hypocellular. The testes were absent, and there was a lobular pneumonia.

Comment: This patient, who was a eunuch, had had pancytopenia for 20 years but needed transfusions only during the first three years and the last five months of his illness. He was symptomatically improved on testosterone therapy, but showed no clear-cut hematologic response. In spite of the long duration of his illness and the presence of moderate hemosiderosis at autopsy, he did not fulfill the criteria used in this study for exogenous hemochromatosis (table 4).

Case 50. A 20 year old white male was admitted to the University of Virginia Hospital November 22, 1938, with a four-week history of an upper respiratory infection, nosebleeds, weakness and fever. Several years prior to admission he had been told that his white count was low, but had had no symptoms suggestive of anemia until the present illness. There was no history of toxic exposure, and he had received no medication except iron.

On physical examination the temperature was 103° F., and the skin was pale. Purpuric lesions and retinal hemorrhages were prominent. There was generalized

* This patient is case 24 in the series reported by Bomford and Rhoads.[8]

lymphadenopathy, and the spleen was palpable just beneath the costal margin. The liver was not felt.

Admission blood values were: hemoglobin, 25%; red cell count, 1.1 million per cu. mm.; reticulocytes, 0.2%; white cell count, 2,800 per cu. mm. with 4% band forms, 3% segmented forms, and 93% lymphocytes; platelet count, 11,300 per cu. mm. Bone marrow aspirated from the sternum was hypocellular and contained no megakaryocytes and only a rare nucleated red cell. The differential count of the bone marrow showed 28% blasts, 35% myelocytes, 1% metamyelocytes, 2% band forms, 1% segmented forms, 8% lymphocytes and 25% unclassified cells.

Course: The patient ran a septic course, and blood cultures were positive for *B. proteus*. He had frequent episodes of nosebleeds and one episode of hematemesis. He became steadily worse in spite of transfusions, and died on November 29, 1938, one week after admission and five weeks after the onset of symptoms. His white count fell to 200 per cu. mm. terminally.

Autopsy: The autopsy was limited to examination of the abdominal contents. There were generalized ecchymotic areas of the abdominal viscera. The liver weighed 1,820 gm., the spleen weighed 770 gm., and there was moderate enlargement of the mesenteric and retroperitoneal lymph nodes. Microscopic examination of the liver showed nothing suggestive of leukemia, and only a few myeloid cells were visible in sections of the spleen and lymph nodes. No red cell precursors or megakaryocytes were present in the bone marrow obtained from the femur and vertebrae, which was markedly hypocellular and appeared gelatinous and atrophic. A diagnosis of aplastic anemia was made.

Comment: This patient had a rapidly fatal course, thought to be due to acute aleukemic myelocytic leukemia because of the generalized lymphadenopathy, splenomegaly, and increased numbers of blasts in the bone marrow, but at autopsy was found to have aplastic anemia.

Summary

1. Fifty cases of aplastic anemia, varying in age from four years to 82 years, have been analyzed.

2. Toxic exposure was thought to be the etiologic agent in seven patients, while the cause was unknown in 43.

3. Most of the patients had pancytopenia, a macrocytic anemia, relative lymphocytosis, and a hypocellular bone marrow. However, in 13 the bone marrow was normocellular or hypercellular, and seven patients had anemia that was not associated with leukopenia or thrombocytopenia.

4. Although the most important factor in the anemia in these patients was deficient erythrocyte production, the presence of an associated hemolytic component manifested by increased fecal urobilinogen excretion and mild reticulocytosis was not unusual.

5. Exogenous hemochromatosis was found in six of the 14 autopsied patients. Brownish gray skin pigmentation, lymphadenopathy, hepatomegaly and splenomegaly occurred commonly in patients who received multiple transfusions.

6. The prognosis was most favorable in patients with anemia alone and in those with a hypercellular bone marrow. However, an illness of long duration was not uncommon in those with pancytopenia and a hypocellular

bone marrow. Although 12 of the 37 patients who presented with pancytopenia died within a year, six lived more than five years, and one survived 20 years.

7. A complete remission occurred in six patients, and a partial or temporary remission in another six patients. Both the spontaneous remissions and those that followed corticosteroid therapy and splenectomy occurred most often in patients who had anemia alone.

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SUMMARIO IN INTERLINGUA

Esseva analysate 50 casos de anemia aplastic. Le etates del patientes variava inter quatro e 82 annos. Le serie includeva 35 masculos e 15 femininas. In 43 del casos, nulle causa pro le anemia poteva esser trovate. In le remanente septe, exposition toxic esseva reguardate como un factor etiologic. Le agentes incriminate esseva benzol, phenylbutazona, Mesantoina, un agente vaporisatori arseniose, e chloramphenicol.

Le majoritate del patientes se presentava con pancytopenia, un anemia macrocytic, lymphocytosis relative, e hypocellularitate del medulla ossee. Tamen, in 13 casos le medulla ossee esseva normo- o hypercellular, e septe patientes habeva anemia non associate con leucopenia o thrombocytopenia. Vinti-septe patientes habeva augmentate procentages de lymphocytos in le medulla ossee.

Ben que le factor le plus importante in le anemia de iste patientes esseva un inadequate production de erythrocytos, le presentia de un associate componente hemolytic—manifeste in augmentos del excretion de urobilinogeno fecal e in leve grados de reticulocytosis—non esseva inusual.

Pigmentation cutanee de color brunastre-gris, lymphadenopathia, hepatomegalia, e splenomegalia occurreva communmente in patientes qui recipeva transfusiones multiple. Hemachromatosis exogene esseva constatate in sex del 14 patientes necropsiate.

Le prognose esseva le plus favorabile in patientes con anemia sol e in illes con hypercellularitate de medulla ossee. Tamen, un curso prolongate del morbo non esseva incommun in patientes con pancytopenia e hypocellularitate del medulla ossee. Ben que 12 del 37 patientes presentate con pancytopenia moriva intra un anno, sex superviveva plus que cinque annos, e un superviveva 20 annos. Infection esseva le causa de morte le plus commun in le gruppo integre, sed inter le patientes con thrombocytopenia, hemorrhagias causava le plus grande numero de mortes.

Trenta-quatro patientes esseva tractate con corticosteroides. Sex de istes habeva un remission, nove exhibiva melioration, e 19 habeva nulle responsa. Splenectomia esseva effectuate in cinque patientes, con remission complete in un caso, con melioration in duo, e sin responsa in le remanente duo. A parte iste remissiones, tres patientes experientiava remission spontanee. Tanto le remissiones spontanee como etiam le remissiones post corticosteroides e splenectomia occurreva le plus frequentemente in patientes qui habeva anemia sol.

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THE PHYSIOLOGIC AND CLINICAL SIGNIFICANCE OF ERYTHROPOIETIN *

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UNTIL recently it was generally agreed that low oxygen tension in the bone marrow constituted a direct stimulus for red cell production. This view was challenged by many investigators whose studies demonstrated that the rate of erythropoiesis, both in vivo [1, 2] and in marrow cultures,[3, 4] was independent of changes in oxygen tension. Clearly an alternate hypothesis was needed.

In 1906 Carnot and Deflandre described the erythropoietic-stimulating properties of serum of anemic rabbits by injecting this serum into normal rabbits, thereby obtaining increased reticulocyte and hemoglobin values in the animals that received the anemic serum.[5] This experimental procedure was employed by Borsook and his co-workers,[6] who found the stimulating properties remained even after the bulk of the protein had been removed by heat denaturation. By testing extracts of anemic rabbit plasma in rats, these workers demonstrated that species barriers could be crossed.

Our investigations have been concerned with the role of a humoral substance or group of substances in the regulation of red cell formation in health and disease. Our results, in conjunction with the findings of other investigators,[5-23] point to a theory of the regulation of erythropoiesis which may be stated as follows: In animals and man, erythropoiesis is regulated continuously by a humoral substance or group of substances referred to as erythropoietin. In this presentation, we will outline briefly some of the evidence for this theory that has been derived from animal investigations and some results of clinical studies on anemic patients. In the present state of knowledge we find it convenient to use the term erythropoietin, first suggested in 1948 by Bonsdorff and Jalivisto,[7] although it is quite possible that more than one erythropoietic-stimulating factor exists. Indeed, recent investigations suggest that there are at least two distinct erythropoietic-stimulating factors.[18, 19]

Erythropoietin can be demonstrated in plasma by a number of bio-assay procedures. To measure increases in the red cell, hemoglobin, or reticulocyte values or in marrow erythroid cellularity following multiple injections of plasma or serum is time-consuming, and unless many injections are given the changes are often too small to be significant. When an intravenous

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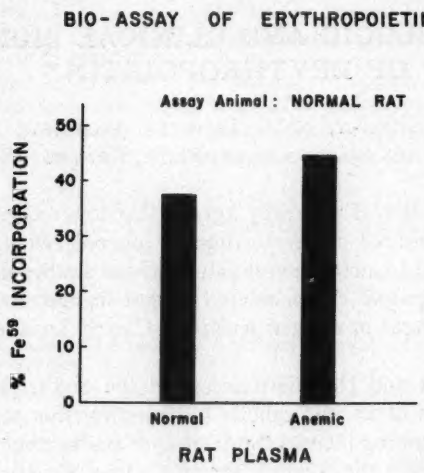

FIG. 1.

tracer dose of Fe^{59} is administered to rats that have previously been given two daily injections of anemic rat plasma, the iron incorporated into newly-formed red cells in the peripheral blood 16 hours later is greater than that found in rats injected with normal rat plasma.[11] The difference in Fe^{59} incorporation in the peripheral red cells, summarized in figure 1, represents the erythropoietic-stimulating property of the anemic plasma. Although this difference is readily reproducible, and highly significant when four or more rats are used in each group, the difference is small in relation to the large amount of radioiron incorporated into the red cells following injections

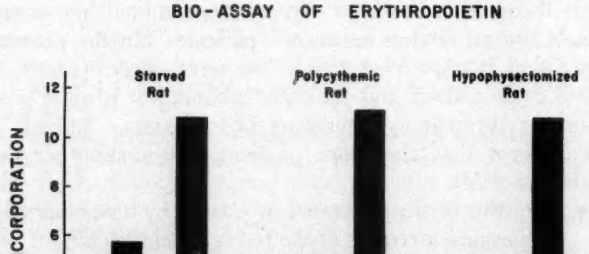

FIG. 2.

of normal plasma or physiologic saline. Figure 2 shows that the sensitivity of the assay is increased if, by any of a number of procedures, the rate of erythropoiesis is depressed in the animals prior to assay. Depression can readily be accomplished by hypophysectomy, starvation or transfusion.[12, 13] Following these alterations, red cell production is almost completely halted in the assay animals, but they maintain their ability to respond to plasma or plasma extracts rich in erythropoietin. It is therefore reasonable to attribute the suppression of erythropoiesis to a decreased erythropoietin content in the

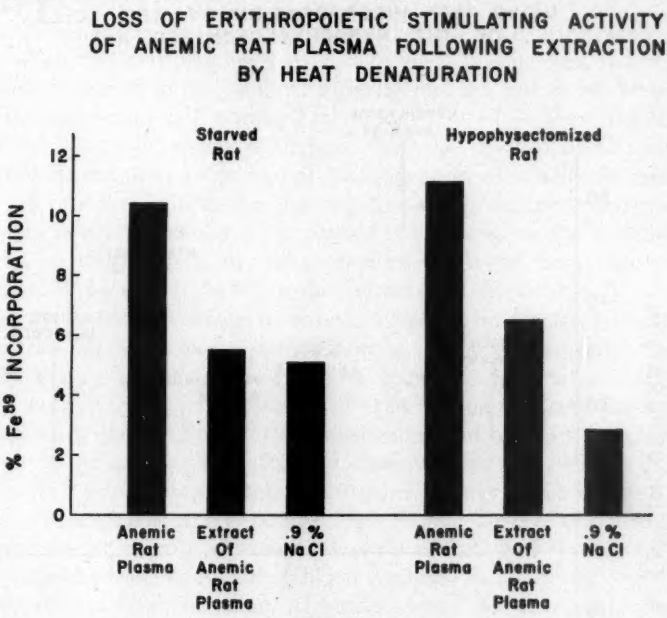

FIG. 3.

assay animals. It has also been shown in our laboratories that the well known polycythemia produced by multiple injections of cobaltous chloride is accompanied by, and we believe is the consequence of, an increased erythropoietin titer.[20, 21]

About two years ago we first turned our attention to an investigation of erythropoietin in man. The complete separation of erythropoietin from plasma has not yet been accomplished, but since Borsook and co-workers [6] demonstrated that the boiled extract of rabbit plasma stimulated erythropoiesis in rats, we initially employed the same method of partial purification of human plasma, removing the bulk of the plasma proteins by heat denaturation. Again, the basis of the assay employed was the Fe^{59} incorporation by the red cells of hypophysectomized rats. With the use of this procedure it was shown that plasma from patients with hypoplastic anemia, leukemia,

pernicious anemia, drug-induced hemolytic anemia and acute gastrointestinal hemorrhage contained elevated titers of erythropoietin.[17] Erythropoietin-stimulating activity can be demonstrated in normal plasma if, after removal of the bulk of the protein by either heat denaturation or perchloric acid precipitation, the extract is concentrated tenfold.[17] During this phase of the investigation we were troubled by a number of negative assays when positive

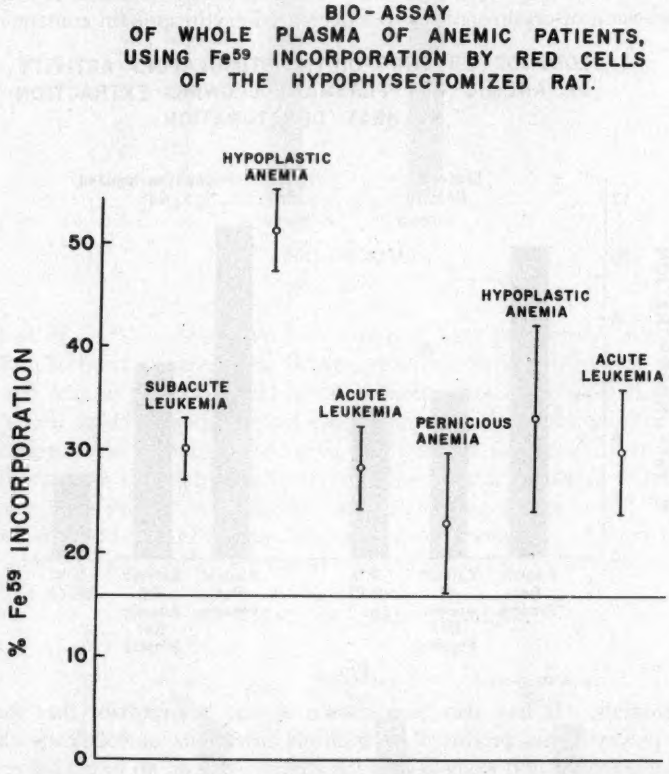

FIG. 4.

results were anticipated. We therefore studied the loss of erythropoietin during the preparation of a heat-denatured plasma extract. For this we first used experimental animals. Figure 3 shows the magnitude of the loss of erythropoietin when the erythropoietic-stimulating properties of plasma of rats, previously bled to a hematocrit of 25%, are compared with a heat-denatured extract of the same anemic plasma. Comparable losses are encountered when other methods of protein removal are substituted for heat denaturation. Hence, the erythropoietic-stimulating property of whole plasma obtained from anemic patients was compared with that of the heat-

denatured extract of the same plasma. In many instances, plasma samples were clearly positive when tested directly but failed to differ significantly from control values after extraction. Control values were established by assaying whole plasma from 10 normal donors in 50 hypophysectomized rats. An average Fe^{59} incorporation of 9.2% (1 standard deviation = 3.2%) was obtained, and it is reasonable to assume any plasma is positive for erythropoietin if the average Fe^{59} incorporation exceeds 15.6%, the average normal value plus 2 standard deviations.

Figure 4 shows the results of the assay of plasma from six anemic patients. The data are of particular interest because a negative result was obtained when the heat-denatured extract of their plasma was tested. Each plasma was assayed in five or more animals, and the results are plotted here as an average value ± 1 standard deviation. In all of these instances the results of bio-assay strongly suggest that the erythropoietic-stimulating properties exceed those of normal plasma, the assay of which averages 9.2%. In considering the significance of a negative assay, one must thus be aware of the loss of erythropoietin if the plasma is subjected to fractionation prior to assay. Unfortunately, in our experience the losses have been variable, regardless of the care with which the extracts are prepared.

The dynamic relationship between erythropoietin levels and severity of anemia can be seen in patients following blood transfusion. In three severely anemic patients whose plasma contained high titers of erythropoietin, we were able to demonstrate a rapid decline to levels that could not be measured within 24 hours after transfusions had brought the hemoglobin to 10 gm.% or more. We have also confirmed the experiments of Piliero et al.[14] which demonstrated high erythropoietin titers in the urine of anemic patients whose plasma also contained high titers. In the one patient whose urine was studied serially, a prompt fall in the excretion of erythropoietin was noted on three occasions following blood transfusions. Figure 5 shows data obtained on one such occasion. Initially, when the hemoglobin was 3.2 gm.%, the erythropoietin titer of the plasma, even after extraction, was high. Transfusions raised the hemoglobin above 10 gm.%, and the erythropoietin titer of the plasma extract had fallen to a low level. Several 24-hour urines were collected and prepared for assay by dialysis and twenty-fold concentration. The results of assay, corrected by subtracting saline control values, are expressed as vertical bar-graphs, and the trend appears to be one of decreased urinary excretion of erythropoietin as the hemoglobin rises.

To date, seven plasma specimens from patients with refractory anemia secondary to chronic renal disease have been investigated. In no instance was even a slight elevation of the erythropoietin titer found on assay of either the boiled plasma extract or the whole plasma.

Another interesting observation is worthy of comment. The greatest stimulation of erythropoiesis in rats is induced by anemic plasma or plasma extracts from patients whose marrow showed the least erythropoiesis—for

example, from patients with hypoplastic and aplastic anemia, erythrogenesis imperfecta, and leukemias. On the other hand, assay results of plasma from patients with more active erythropoiesis in the marrow—e.g., hemolytic anemia, pernicious anemia, acute gastrointestinal hemorrhage—are less spectacular and often nonpositive. The possibility of marrow degradation

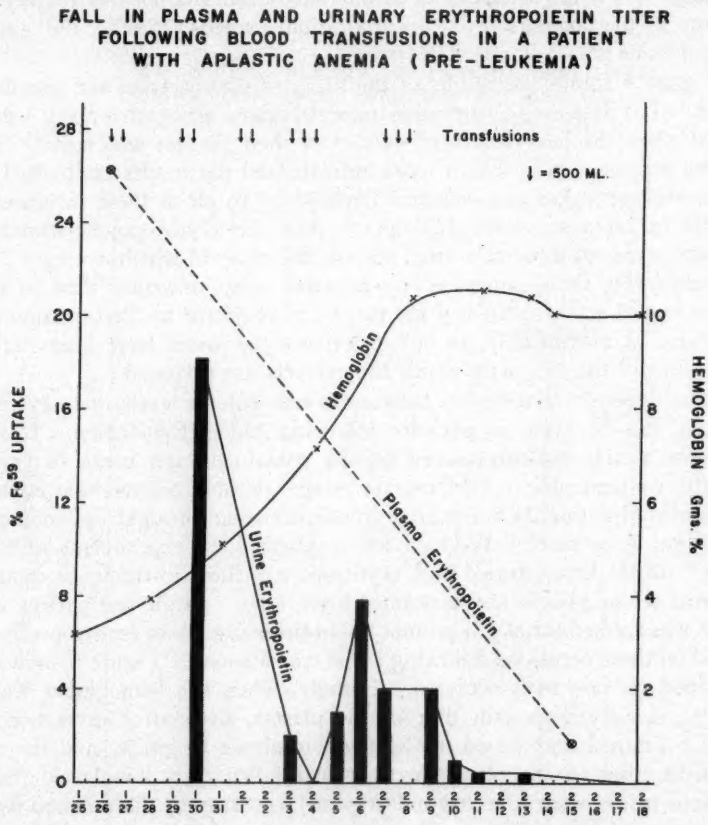

FIG. 5.

or utilization of erythropoietic-stimulating factor therefore remains for future investigation. Evidence for erythropoietin utilization during erythropoiesis in experimental animals has been presented by Stohlman.[22]

In summary, the animal investigations indicate that erythropoietic-stimulating hormones are necessary for and regulate the rate of erythropoiesis. By concentrating extracts of normal human plasma, one can demonstrate erythropoietic-stimulating properties in normal plasma. Without concentrating plasma from patients with hemoglobin values of less than 8 gm.%, one can frequently demonstrate erythropoietic-stimulating properties. Since,

however, this assay system is not sufficiently sensitive to demonstrate erythropoietin in normal plasma without concentration, a negative assay of unconcentrated plasma or plasma extracts indicates only that the expected high titer, considering the degree of the patient's anemia, is not present. This, however, does not indicate that any or all of these anemias can be attributed to decreased erythropoietin titers. Data from experiments on animals, coupled with clinical observations, suggest that some cases of anemia that are associated with chronic renal disease, malnutrition, chronic infection and rheumatoid arthritis, all reported on occasion to be responsive to cobalt administration, [24, 25, 26, 27, 28] might be attributed to erythropoietin deficiency. Confirmation of this speculation, however, must await a more sensitive assay system and more efficient purification procedures, or perhaps the isolation of erythropoietin in a form sufficiently potent and pure to justify clinical trials in anemias of obscure etiology. It would appear that the clinical applicability of erythropoietin will be primarily to any individual who becomes anemic because he fails to maintain adequate levels of erythropoietin, or is not able to respond to anemia by increased production of erythropoietin.

Summario in Interlingua

Investigationes animal indica que le processo erythropoietic depende del effecto stimulatori de certe hormones. Iste hormones, designate como erythropoietina, es necessari pro le erythropoiese e regula su intensitate. Erythropoietina pote esser demonstrate in plasma o extractos de plasma e in extractos de urina per mesurar le effecto que duo injectiones de tal preparatos exerce super le erythropoiese in rattos. Le intensitate del erythropoiese in le animales experimental es determinate per mesurar le incorporation, post 16 horas, de un dose traciatori de Fe^{59} in le erythrocytos circulante. Le sensibilitate del essayo es augmentate si le erythropoiese es primo deprimite per hypophysectomia, affamation, o transfusion. Per concentrar extractos de normal plasma human, on pote demonstrar proprietates erythropoietinic in le plasma normal. Sin concentrar le plasma on pote, frequentemente, demonstrar tal proprietates in specimens ab patientes con hemoglobina de minus que 8 g pro cento. Le interpretation de essayos negative require alte grados de circumspection, specialmente proque grande e variabile quantitates de erythropoietina es perdite in le manovras extractori. Viste que cobalt se ha monstrate capace a producer polycythemia per augmentar le titro de erythropoietina, il es a expectar que selegite patientes con anemias secundari a nephritis, affamation, neoplasma, o arthritis rheumatoide va forsan responder favorabilemente al administration de erythropoietina.

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A NEW THEORY OF INTERFERENCE WITH THE CLOTTING MECHANISM: THE COMPLEXING OF EUGLOBULIN WITH FACTOR V, FACTOR VII AND PROTHROMBIN * †

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INTRODUCTION

A NEW theory of interference with the clotting mechanism was recently advanced by the authors, based on the observation that unusual plasma globulins complex with and/or coprecipitate clotting factors.[12, 13] The consequence is a reduction or inactivation of clotting factors, resulting in hemorrhagic disorders of varying degree. In addition, an unstable clotting mechanism and/or increased local concentrations of clotting factors would result, causing an increased thrombotic tendency. This theory offers a reasonable explanation for bleeding diatheses such as occur in purpura hyperglobulinemica, macroglobulinemia, multiple myeloma, liver damage and other conditions characterized by production of unusual plasma globulins. It can also explain the less frequent simultaneous thrombotic tendency present in some of these disorders.

In this paper, data are presented derived from studies of three cases, two of macroglobulinemia and one of myocardial infarction. There was a dual thrombo-hemorrhagic diathesis in the case of myocardial infarction and in one case of macroglobulinemia, and a hemorrhagic diathesis in the second case of macroglobulinemia. The coexistence of these seemingly contradictory potentialities is emphasized. In these cases the unusual protein was a euglobulin, and the clotting factors interfered with were Factor V and, to a lesser extent, prothrombin and Factor VII. These data are consistent with and lend further support to the postulated theory.

MATERIALS AND METHODS

1. *Precipitation of euglobulin* was accomplished by the addition of water to the plasma. In case 1 four volumes and in cases 2 and 3 nine volumes were required. The precipitated protein was centrifuged down, washed

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three times with 10 volumes of twice-distilled water, and made to 0.9% sodium chloride in the original plasma volume. The clotting activity of plasma after the precipitation and reconstitution of the euglobulin was unchanged, provided no appreciable time elapsed. Therefore, control plasmas were treated in a manner identical to and for the same length of time as the experimental plasmas.

2. *Specific viscosity* was measured in a 30 second Ostwald viscometer mounted in a water bath of appropriate temperature.

3. *Electrophoresis* was performed in a Durrum-type paper electrophoresis apparatus. The strips were stained with bromphenol blue and quantitated with a photovolt densitometer.

4. *Protein concentrations* were determined by the method of Lowry et al.,[24] using standards prepared from a 40/60 w/v mixture of human gamma globulin and bovine albumin.

5. *Fibrinogen* was measured by the Jacox detergent method.[15]

6. *Factor V* was measured by the one-stage method of Lewis and Ware.[20] The substrate was aged normal plasma.

7. *Factor VII* was measured by the one-stage method of Owren as described by Tocantins.[33] The substrate was asbestos-filtered normal plasma.

8. *Prothrombin* was measured by the one-stage method of Ware and Stragnell.[30] All dilutions were made with 0.9% sodium chloride, and the standard curve was constructed from the average results with five normal plasmas.

This method was also used as a two-stage procedure for prothrombin. Plasma samples were diluted from 1:50 to 1:250 with saline, and incubated with the thromboplastin-calcium for increasing periods of time. The prothrombin-free beef plasma was then added and the clotting time determined. The minimal clotting time was taken as an index of activity. Standard concentration curves were constructed from the minimal clotting times of five pooled normal plasmas. With the use of this method the effects of accelerator factor activities were minimized or eliminated.

Prothrombin activity of the euglobulin solutions was also measured by this two-stage procedure. It was frequently necessary to use the euglobulin solution undiluted in order to obtain clotting. Since the calibration curves were constructed upon diluted plasma, the wide difference in chemical composition between the standards and the euglobulin solutions could introduce uncontrollable errors. It appeared, however, to give reasonable values preferable to those obtained by one-stage methods.

9. *Total accelerator activity* was also measured by the same two-stage procedure. A standard curve was constructed from the time of incubation necessary for five pooled normal plasmas in various dilutions to reach minimal clotting time, i.e., maximal thrombin production.

10. *Plasma* was prepared using dry balanced oxalates as the anticoagulant, and care was taken to add the exact volume of blood for the amount

of oxalate. Samples were stored at −20° C. In case 1 the patient died while the work was in progress. Clotting tests were therefore run on frozen samples. When comparative tests were run the normal controls used were similarly frozen. Both fresh and frozen plasmas were used for clotting tests in cases 2 and 3.

Case Reports

Case 1. A 52 year old man, when first seen in April, 1954, gave a one-year history of anemia unresponsive to iron therapy. The spleen tip was palpable 8 cm. below the costal margin. The blood count was: red blood cells, 2.84 million; hemoglobin, 8.3 gm.%; packed cell volume 28%; white blood cells, 13,800, with polymorphonuclears, 45%; lymphocytes, 49%; mononuclears, 3%; eosinophils, 3%; reticulocytes, 0.10%; platelets, 410,000. Rouleaux formation was marked, and the sedimentation rate was 49 mm./hr. (Westergren). Bone marrow from the left ilium was of normal cellularity and contained 40% small lymphocytes. Total protein was 9.86 gm.%. There were no cold agglutinins, auto-agglutinins or iso-agglutinins, and the Coombs' test was negative. A temporary reduction in the size of the spleen resulted from x-ray therapy. In August, 1955, the patient suddenly developed edema of the left leg with multiple small hemorrhages into the skin below the knee. At this time platelets were 196,000. The anemia became progressively more severe and was not ameliorated by either Acthar Gel or Meticorten. The sedimentation rate was extremely variable and ranged between 15 mm. and 110 mm./hr. (Westergren). The bone marrow contained 50% small and medium lymphocytes but no unusual numbers of plasma or reticuloendothelial cells. The total protein rose to 13.0 gm.%. Plasma and serum specific viscosity was 15 times normal at 37.5° C., and increased to 40 times normal at 4° C. Sodium chloride added to 1.25 times physiologic concentration nullified the viscosity increase. On ultracentrifugation there was a major component at $S_{20} = 18.4$, and two lesser components at $S_{20} = 25.8$ and 33.0.

In October, 1955, because the red count had fallen to 1.97 million and the hemoglobin to 5.8 gm.%, the patient was given one unit of packed red cells. This was followed within hours by dyspnea and marked weakness. He was hospitalized and transfused four times over a period of several days. In spite of this, he deteriorated rapidly, developed a fever of 104° F., hemorrhaged extensively from the mouth, and on November 1, 1955, became comatose and died. Autopsy, restricted to the abdomen, showed plasma cell infiltration of the liver, lymph nodes and vertebral bone marrow. The inferior vena cava and left common iliac vein were almost totally occluded by a solid gray thrombus.

Summary: This is a case of macroglobulinemia with a dual thrombohemorrhagic diathesis characterized by purpura, oral hemorrhages and thrombosis of a major intra-abdominal vein.

* *Case 2.* A 60 year old man was first seen in 1951 for a complaint of dizziness. Physical examination revealed only moderate hepatomegaly. Routine laboratory studies were negative.

In 1953 the patient passed bloody stools. A benign polyp of the transverse colon was found and removed. The hepatomegaly still persisted, and a history of heavy alcohol intake was elicited. The blood counts were normal. Cephalin flocculation was 4 plus in 24 hours, thymol turbidity was 13 units, and the bromsulfalein dye retention was 10% in 45 minutes.

* The authors wish to thank Dr. M. Yettra and Dr. S. Zemer, of the Southern California Permanente Medical Group, for the opportunity to study this case.

In April, 1956, the patient complained of malaise, cough and sweating which were attributed to "flu." Again the blood counts and urinalysis were normal. In September, 1956, he had a subconjunctival hemorrhage. A month later he evidenced weakness and anorexia, and on November 5, 1956, was admitted to the hospital. At this time moderate hepatosplenomegaly was noted. Red blood cells were 3.4 million; hemoglobin, 9.7 gm.%; white blood cells, 9,200; the differential count showed slight lymphocytosis. Rouleaux formation was marked. The urine had a moderate number of white cells which disappeared without specific treatment. There was no Bence Jones protein, and urobilinogen excretion was normal. Serologic tests for syphilis and bilirubin were normal. Total protein was 8.27 gm.%, with 1.7 gm.% albumin and 6.57 gm.% globulin. Electrophoresis showed a gamma 2 globulin fraction of 4.42 gm.%. Cephalin flocculation was 4 plus in 24 hours, and thymol turbidity was 17.7 units. Prothrombin was 36%. The serum was observed to gel at low temperatures. X-rays of the skull and chest were normal, and an upper gastrointestinal series showed thickening of the gastric mucosa. The bone marrow showed atypical lymphoid forms and large lymphoid follicles which appeared to be infiltrating a hypoplastic marrow. The patient was transfused and discharged, symptomatically improved.

Petechiae were subsequently noted over the lower legs on several occasions. Until March, 1957, frequent small nosebleeds occurred.

In March, 1957, the patient complained of sensitivity to cold in his hands and feet, and of slight transient deafness. At this time the total protein was 10.3 gm.%, of which 53% (5.45 gm.%) was a euglobulin with a single electrophoretic component in the gamma globulin region. Plasma viscosity was 40 times normal at 37.5° C., and impossible to measure at lower temperatures. It was unaffected by sodium chloride or albumin. Ultracentrifugation showed a range of values for plasma S constants in the macroglobulin region. Prothrombin was 68%; Factor V, 114%; Factor VII, 21%; prothrombin consumption, 68%; fibrinogen, 355 mg.%.

The patient has recently noted blurring of vision, and the fundi at this time showed many flame-shaped hemorrhages, occasional white exudates, some arteriolar narrowing and irregular venous engorgement. Treatment has consisted chiefly of transfusions, of which he has received 20 to date. He was also given 40 mg. prednisone daily for four months, which reduced somewhat the size of the spleen but did not affect the anemia.

Summary: This is a case of macroglobulinemia with a hemorrhagic diathesis characterized by nosebleeds, fundal and subconjunctival hemorrhages, and purpura over the lower extremities.

Case 3. A 49 year old man was admitted to the hospital in March, 1956, suffering from severe epigastric pain which radiated to the left shoulder and neck. A diagnosis of anterior myocardial infarction was established. He was treated with heparin and Dicumarol and recovered uneventfully. The urine showed 4 plus albumin and innumerable red cells.

On February 18, 1957, the patient was re-admitted to the hospital with dyspnea of four days' duration, and severe chest pain radiating to both shoulders. The liver was 8 cm. below the costal margin and was hard and nodular. The urine had 2 to 5 red blood cells per high power field, and occasional pus and epithelial cells. Hemoglobin was 12 gm.%; white blood cells, 10,800, with polymorphonuclears, 75%; bands, 2%; lymphocytes, 20%; mononuclears, 3%. The sedimentation rate was 56 mm./hr. (uncorrected Wintrobe). Prothrombin was 60%. Total protein was 6.2 gm.%, with 3.3 gm.% albumin and 2.9 gm.% globulin. Thymol turbidity was 12 units, and cephalin flocculation was 3 plus. The transaminase test was normal, and

the electrocardiogram showed no fresh damage. Chest x-rays showed congestive heart failure. The patient had diffuse purpura on both legs to the groin. He was not given anticoagulants but was treated with digitoxin and nitroglycerin, with improvement.

The patient was again admitted to the hospital on March 12, 1957, with umbilical pain and a recurrence of the chest pain. At this time he had 2 plus ankle edema. Purpura was present, symmetrically distributed over both feet and legs. The liver was soft, tender and flat, and extended 6 cm. below the costal margin. The blood count was: hemoglobin, 8.2 gm.%; white blood cells, 7,100, with polymorphonuclears, 76%, and lymphocytes, 24%. Platelets appeared to be normal in number and morphology. The sedimentation rate was 23 mm./hr. (corrected, Wintrobe). Clotting time was one and one-half to two minutes; bleeding time, one and one-half minutes; prothrombin concentration, 58%. Fibrinogen was 590 mg.%. The Rumpel-Leede test was positive, with 10 to 15 petechiae per square inch. Serologic test for syphilis was weakly positive. Repeated blood cultures were negative. Total protein was 6.5 gm.%, with 3.1 gm.% albumin and 3.4 gm.% globulin. Plasma viscosity was slightly elevated. Icteric index was 7 units; thymol turbidity, 17 units; cephalin flocculation, 4 plus. The electrocardiogram and chest x-rays were unchanged. The urine showed 2 plus albumin and occasional red blood cells, white blood cells, and hyaline and fine granular casts. The patient was given digitalis. During hospitalization the purpura first disappeared and then re-appeared, spreading gradually over his entire body. On the morning of March 25 he complained of severe nausea and retching, and died that afternoon.

At autopsy an enlarged liver with the classic picture of chronic passive congestion was found. The spleen had a depressed scar consistent with an old infarct. Examination of the heart revealed arteriosclerosis of the coronary arteries with an old myocardial infarct and bacterial endocarditis of the aortic valve.

Summary: This is a case which is not macroglobulinemia, in which there is a thrombo-hemorrhagic diathesis characterized by purpura and renal bleeding, and both splenic and myocardial infarcts.

Experimental Results

The common feature of these three cases is that each had a plasma euglobulin which on precipitation by dilution complexed with and precipitated clotting factors.

In case 1 the euglobulin was a macroglobulin which comprised 57% (7.4 gm.%) of the total protein and had a single electrophoretic component in the gamma globulin region. Various clotting tests were run on the patient's plasma before and after the euglobulin was removed and on the euglobulin solution. In table 1, section 1, a solution of the euglobulin was added to a fibrinogen substrate with and without calcium, thromboplastin, or both. Clotting of the euglobulin solution occurred only in the presence of all three added reagents, indicating the presence of prothrombin and probably accelerator factors, but not of thrombin. In table 1, section 2, it is shown that normal plasma after the addition and reprecipitation of the euglobulin had a prolonged clotting time. This confirmed the ability of the euglobulin to complex with and remove clotting factors. It also indicated that the abnormality was in the euglobulin and not in the clotting factors.

The addition of euglobulin to normal plasma had no inhibitory effect on the prothrombin or accelerator factor activity. In table 1, section 3, the one-stage prothrombin method was applied to normal plasma, normal plasma after the addition and reprecipitation of the euglobulin, the patient's plasma, euglobulin-free plasma and euglobulin solution. Clotting factors were removed from both the patient's and normal plasma by the euglobulin, and clotting factors were demonstrable in the euglobulin solution. Results

TABLE 1

Clotting Characteristics of Plasma, Euglobulin-Free Plasma and Euglobulin Solution (Case 1)

Sec.	Test System	Material Added to Test System	Clotting Time (Seconds)	Interpretation
I	Fibrinogen	Eugl. Sol. +Ca	No clot	No thrombin in euglobulin solution.
		Eugl. Sol. +Tp	No clot	
		Eugl. Sol. +Tp+Ca	110	Prothrombin present in euglobulin solution.
II	Recalcified clotting	Normal Plasma	80	Euglobulin removes clotting factors from normal plasma.
		Normal Plasma after euglobulin addition and reprecipitation	315	
III	Prothrombin (Quick)	*Normal Plasma	37	Euglobulin removes prothrombin from normal plasma.
		*Normal Plasma	60	
		Patient's Plasma 10/10	50	Euglobulin removes prothrombin from patient's plasma which is demonstrable in euglobulin solution.
		Patient's Eugl.-free Plasma	208	
		Patient's Eugl. Sol.	39	
		Patient's Plasma 10/31	115	
		Patient's Eugl.-free Plasma	245	
		Patient's Eugl. Sol.	47	
IV	Prothrombin (Ware-Stragnell) (1-stage)	Normal Plasma	57	Euglobulin removes prothrombin and possibly accelerator factors from normal plasma.
		4 Normal Plasmas after euglobulin treatment	93–114	
		Patient's Plasma 10/10	42	Euglobulin removes prothrombin and possibly accelerator factors from patient's plasma. Prothrombin is demonstrable in euglobulin solution.
		Patient's Eugl.-free Plasma	69	
		Patient's Eugl. Sol.	118	
		Patient's Plasma 10/31	81	
		Patient's Eugl.-free Plasma	216	
		Patient's Eugl. Sol.	276	
V	Accelerator factors (Ware-Stragnell) (2-stage)	Eugl. Sol. Incubation Time (Min.)		
		0	248	Prothrombin and accelerator factors are present in euglobulin solution.
		1	157	
		2	58	
		3	50	
		4	55	

Ca—Calcium.
Tp—Thromboplastin.
Eugl.—Euglobulin.
* The same samples as were used in Sec. 2.

shown in table 1, section 3 were confirmed by the two-stage prothrombin method as shown in table 1, section 4. The presence of both prothrombin and accelerator factors in the euglobulin solution is shown in table 1, section 5.

The removal of both accelerator factor activity and prothrombin by precipitation of the euglobulin is shown graphically in figure 1, which also illustrates how the two-stage prothrombin test was used for these determinations. The necessity for a longer incubation time of the euglobulin-

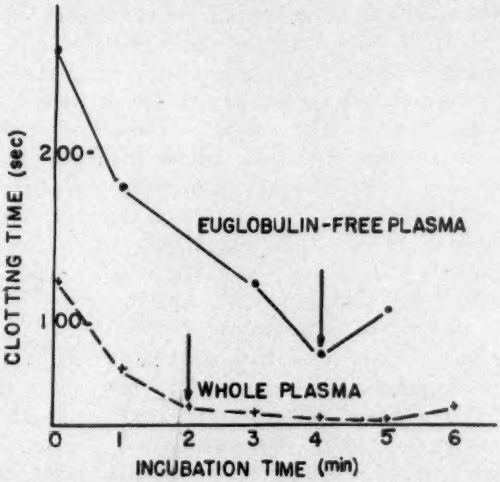

FIG. 1. Effect of euglobulin on prothrombin and total accelerator factors.

free plasma to reach maximal thrombin activity is indicative of reduced accelerator factor activity. The longer clotting time at maximal thrombin activity is indicative of a reduced concentration of prothrombin. Similar results were obtained for normal plasma when the euglobulin was added and reprecipitated.

In case 2 the euglobulin was also a macroglobulin, which comprised 53% (5.45 gm.%) of the total protein and also had a single electrophoretic com-

TABLE 2

Clotting Characteristics of Plasma, Euglobulin-Free Plasma and Euglobulin Solution (Case 2)

Sample	Treatment	Prothrombin 2-Stage (%)	Total Accelerator Factors (%)	Factor V (%)		Factor VII (%)
Patient's Plasma	Whole	66 57	64 61	114		21
	Eugl.-free	24 27	34 41	13	126	7
	Eugl. Sol.	13 12	Present	113		0
Normal Plasma	Whole—untreated	106	120	78		100
	Whole+Eugl.‡	101	120	88		100
	Eugl.-free*	63	80	52	139	50
	Eugl. Sol.†	11	Present	87		0

* After reprecipitation of euglobulin from normal plasma.
† Solution of euglobulin reprecipitated from normal plasma.
‡ Euglobulin solution added to the normal plasma had no measurable Factor V or Factor VII activity.

ponent in the gamma globulin region. Clotting studies of this case are summarized in table 2. Precipitation of the euglobulin resulted in reduced plasma levels of the prothrombin, total accelerator activity, Factor V and Factor VII. Prothrombin, total accelerator activity and Factor V could be demonstrated in the euglobulin solution. Hence, the data clearly show that euglobulin can combine with and remove these clotting factors from blood. The sum of the Factor V present in the euglobulin solution and in the euglobulin-free plasma (126%) was greater than the amount measured in the native plasma (114%). The explanation of this phenomenon seems to rest in the findings of case 3. Factor VII is of interest in that, of the 21% present in the native plasma, only 7% could be measured in the euglobulin-free plasma and none in the euglobulin.

On the addition of the euglobulin to normal plasma and its reprecipitation, similar reductions in plasma prothrombin, total accelerator activity, Factor V and Factor VII were noted (table 2), indicating again that the abnormal complexing behavior resided in the euglobulin. The curves of clotting activity in the whole plasma and the euglobulin-free plasma were similar to those shown in figure 1, and therefore were not reproduced. One hundred thirty-nine per cent of Factor V was measured in the euglobulin solution and the euglobulin-free plasma, as compared with 88% in the normal plasma containing added euglobulin (table 2). This suggests that the additional Factor V was present in the added euglobulin in an unmeasurable form. Factor VII was reduced by 50% in the euglobulin-free plasma and could not be detected in the euglobulin solution (table 2), suggesting that complexing of the Factor VII with the euglobulin had occurred.

In case 3 the euglobulin amounted to only 5.5% (0.36 gm.%) of the total protein and was not a macroglobulin. It had a single electrophoretic component in the gamma globulin region.

Precipitation of the euglobulin reduced the plasma prothrombin from 59% to 46%, and the amount lost was identified in the euglobulin precipitate (table 3, section 2). Factor VII was low in the native plasma, 57% (table 3, section 1) and 22% (table 3, section 2), and disappeared from the frozen plasma in the course of days. Sample A decreased from 57% to 0% in one day (table 3, section 1), and Sample B decreased from 22% to 0% in seven days (table 3, sections 2 to 6). This change was unexpected, since Factor VII is time-temperature stable. The supposition is strong that Factor VII activity decreased during storage by complexing with euglobulin. However, the opportunity to pursue this question was lost when the patient died.

The changes in Factor V are of paramount interest. Factor V was present in the fresh plasma in normal amounts, 112% (table 3, section 1) and 114% (table 3, section 2). However, after euglobulin precipitation the fresh plasma still contained 112% of Factor V (table 3, section 2) and, most amazingly, the euglobulin solution also contained 112% of Factor V

(table 3, section 2). This finding, reminiscent of similar findings in case 2, suggested that one portion of the Factor V had been complexed with the euglobulin in vivo and was not measurable in the plasma. It was later rendered measurable in the separated euglobulin solution. The initial testing was made on plasma stored frozen for one day. It yielded similar results for Factor V, although at lower levels: whole plasma, 14%; euglobulin-free plasma, 13%; euglobulin solution, 29%. The drop in Factor V from 112% to 14% in frozen plasma 24 hours old is not usual, and suggested complexing in vitro of Factor V with the euglobulin.

TABLE 3

Clotting Characteristics of Plasma, Euglobulin-Free Plasma and Euglobulin Solution (Case 3)

Sec.	Sample	Age of Plasma When Precipitated	Prothrombin 1-Stage (%)	Prothrombin 2-Stage (%)	Total Accelerator Factors (%)	Factor V (%)	Factor VII (%)
I	A—whole	Fresh	58			112	57
	A—whole	1 day		66	100	14	0
	A—Eugl.-free	1 day		56 } 77	60	13 } 42	0
	A—Eugl. Sol.	1 day		21 }	Present	29 }	0
II	B—whole	Fresh	35	59	61	114	22
	B—Eugl.-free	Fresh	35	46 } 64	61	112 } 224	12
	B—Eugl. Sol.	Fresh		18 }	Present	112 }	0
III	B—whole	1 day	45	43	41	98	15
	B—Eugl.-free	1 day	29	37 } 54	41	112 } 229	7
	B—Eugl. Sol.	1 day		17 }	Present	117 }	0
IV	B—whole	2 days	44	52	60	25	11
	B—Eugl.-free	2 days	35	46 } 59	60	29 } 79	12
	B—Eugl. Sol.	2 days		13 }	Present	50 }	0
V	B—whole	3 days	56	68	61	52	14
	B—Eugl.-free	3 days	47	39 } 54	61	46 } 153	7
	B—Eugl. Sol.	3 days		15 }	Present	107 }	0
VI	B—whole	7 days	32	52	42	33	0
	B—Eugl.-free	7 days	21	45 } 59	34	62 } 148	0
	B—Eugl. Sol.	7 days		14 }	Present	86 }	0

On the assumption that the Factor V-euglobulin complex might be reversible, the two refrigerated euglobulin solutions were tested periodically for Factor V activity (table 4, sections 1 and 2). In addition, frozen aliquots of Sample B were precipitated at intervals over a period of a week. The euglobulin solutions from these precipitations were also refrigerated and tested periodically for Factor V activity (table 4, sections 3 to 6). Increased Factor V activity was demonstrable in the euglobulin solutions after one to three days of storage. This could be attributed to release of Factor V from the euglobulin complex (table 4, all sections). The maximal Factor V activity demonstrable in the stored euglobulin solutions was 150% after three days (table 4, section 2). Some fluctuations in Factor V

levels in the whole and euglobulin-free plasmas were found. These were probably due to simultaneous reversible binding of the Factor V by the euglobulin and inactivation of Factor V on standing. It has been our experience that Factor V is extremely unstable in euglobulin solution. A sample of euglobulin solution from case 2 had no measurable Factor V activity after six days of refrigerated storage.

In contrast with the findings in cases 1 and 2 and in the studies previously reported,[18] the addition of this euglobulin solution to and reprecipi-

TABLE 4

Effect of Storage on Factor V Activity of Euglobulin Solutions (Case 3)

Section	Sample	Age of Plasma When Precipitated	Age of Eugl. Sol. When Tested	Factor V (%)			
				Plasma	Euglobulin	Rate of Decline	Calculated Minimum
I	A—Plasma			112			
	A—Eugl. Sol.	1 day	Fresh		29	34.0	400
	A—Eugl. Sol.	1 day	1 day		124		
	A—Eugl. Sol.	1 day	3 days		114		
	A—Eugl. Sol.	1 day	6 days		128		
	A—Eugl. Sol.	1 day	7 days		68		
	A—Eugl. Sol.	1 day	8 days		60		
II	B—Plasma			114			
	B—Eugl. Sol.	Fresh	Fresh		112	21.0	262
	B—Eugl. Sol.	Fresh	1 day		137		
	B—Eugl. Sol.	Fresh	2 days		78		
	B—Eugl. Sol.	Fresh	3 days		150		
	B—Eugl. Sol.	Fresh	7 days		103		
	B—Eugl. Sol.	Fresh	11 days		19		
	B—Eugl. Sol.	Fresh	12 days		10		
III	B—Plasma	1 day		98			
	B—Eugl. Sol	1 day	Fresh		117	27.3*	367
	B—Eugl. Sol.	1 day	1 day		109		
	B—Eugl. Sol.	1 day	2 days		114		
	B—Eugl. Sol.	1 day	9 days		94		
IV	B—Plasma	2 days		25			
	B—Eugl. Sol.	2 days	Fresh		50	32.5	469
	B—Eugl. Sol.	2 days	1 day		114		
	B—Eugl. Sol.	2 days	8 days		144		
	B—Eugl. Sol.	2 days	12 days		14		
V	B—Plasma	3 days		52			
	B—Eugl. Sol.	3 days	Fresh		107	23.5	343
	B—Eugl. Sol.	3 days	7 days		108		
	B—Eugl. Sol.	3 days	11 days		14		
VI	B—Plasma	7 days		33			
	B—Eugl. Sol.	7 days	Fresh		86	25.5	380
	B—Eugl. Sol.	7 days	3 days		125		
	B—Eugl. Sol.	7 days	7 days		23		
					Mean	27.3	371

* Because the sample was exhausted before a minimal value was reached, the mean rate of decline was used in the calculation.

tation from normal plasma did not remove prothrombin, Factor V, Factor VII or total accelerator activities. These results suggest that the euglobulin in this case was completely saturated with clotting factors, while the euglobulins in the four other cases were not (cases 1 and 2).[13]

A minimal value for the Factor V which was bound by the euglobulin can be calculated (table 4). The rate of decline in Factor V during the latter days of storage may be taken as the rate of loss of the Factor V activity over the entire period of storage. The loss per day multiplied by the total number of days of storage extrapolated to the day of zero concentration will yield the amount of Factor V released from combination with the euglobulin. The actual amount of Factor V present may be greater than the calculated value by an amount equal to that remaining complexed with the euglobulin and deteriorating without being released from the complex.

Therefore, in addition to in vivo complexing being demonstrated, the data also indicate that quite enormous quantities of clotting factors, 3.70 times the amount measurable in the blood stream, can be complexed by euglobulin in vivo in a manner predicted by the postulated theory. The Factor V activity released from the euglobulin complex could be either active Factor V or its inactive precursor activated during storage. More recent data indicate the presence of both forms in the euglobulin complex.

Discussion

The three cases presented in this paper support the previously postulated theory of interference with the clotting mechanism by abnormal plasma proteins.[12, 13] These cases were chosen to demonstrate different clinical conditions in which the offending protein was a euglobulin. The clotting factors capable of complexing with the euglobulin were principally Factor V and, to a lesser degree, Factor VII and prothrombin. In other cases,[13, 14] the offending protein was a cryoglobulin which had a greater tendency to selectively complex fibrinogen. The fundamental thesis is that these unusual globulins complex with clotting factors, distorting the clotting mechanism and resulting in the dual defect of both a hemorrhagic and a thrombotic diathesis. This theory offers a reasonable explanation both for many unexplained bleeding and clotting disorders and for the presence of these seemingly mutually exclusive tendencies in the same patient.

Case 1 (macroglobulinemia) had a well established hemorrhagic diathesis, universally recognized as a component of this disease,[33] and, in addition, had a large thrombus of the left iliac vein. Case 2 (also macroglobulinemia) had a hemorrhagic diathesis but no thromboses. Case 3 had a hemorrhagic diathesis, a coronary occlusion and a splenic infarction.

In cases 1 and 2 the macromolecular euglobulins comprised 7.4 gm.% and 5.5 gm.%, and in case 3 the euglobulin, which was of normal molecular size, was 0.36 gm.%. Although the amount of euglobulin in cases 1 and 2 was 15 to 20 times that in case 3, the size of the molecule was of the order

of 10 times as great. In the two previously reported cases [18] the euglobulins of normal size comprised 1.6 gm.% and 0.4 gm.%. Thus, the number of molecules of euglobulin is of the same order in all five cases. These data suggest that the combination of euglobulin with clotting factors is on a molecule-for-molecule basis, and that the size of the macromolecules in cases 1 and 2 had no effect on the complexing ability of the protein. In case 3 the euglobulin, comprising 0.36 gm.%, complexed with 3.7 times the normal amount of Factor V. Therefore, small amounts of unusual globulins can induce large effects on the clotting proteins.

In all three cases evidence is presented that prothrombin and accelerator factors are involved in the euglobulin complex, but it is Factor V which is most significantly bound. At the time case 1 was studied, methods had not been set up to permit evaluation of individual clotting factors. However, the two-stage prothrombin test indicated the involvement of accelerator factors in the euglobulin complex. Marked reduction in plasma Factor V activity in case 2 accompanied precipitation of the euglobulin. Similar behavior was observed in one of the previously reported cases (case 2 [18]). In case 3 the in vivo binding of Factor V to the euglobulin was extraordinary. In this case the plasma contained 112% of demonstrable Factor V and 370% additional Factor V bound to the euglobulin.

Recognition that 370% of Factor V was bound by 360 mg.% of euglobulin (without allowance for the weight of the bound Factor V) suggests that much of the Factor V normally present in plasma could be neutralized or bound by only 100 mg.% of euglobulin. Euglobulins representing as little as 100 mg.% of plasma protein have been precipitated from a variety of plasmas in which clotting defects of minor degree were measurable. With the method of euglobulin separation by water dilution, it is doubtful that the 100 mg.% found represented the entire amount of euglobulin in these plasmas. Amounts of euglobulin of the order of 100 mg.% may be normally present in plasma without detection by this method. Two hundred milligrams per cent of euglobulin in normal plasmas has been found by salting-out technics.[11] These quantitative relationships suggest that Factor V-euglobulin complexes may be a normal mechanism for controlling the Factor V activity in the plasma. This suggestion is supported by the fact that Factor V was stable when complexed with euglobulin. It is also probable that increased euglobulin production represents an augmentation of a normal physiologic mechanism, rather than a specific pathologic response.

The data presented suggest that prothrombin and Factor VII as well as Factor V participate in the euglobulin complex. Coexistent with the peculiarities in the clotting mechanism, there was a hemorrhagic diathesis in case 2 and a dual thrombo-hemorrhagic diathesis in cases 1 and 3. Of particular importance is case 3, in which coronary occlusion was the chief clinical manifestation of the clotting defect. In addition to the myocardial

infarct, there were a splenic infarct, purpura and blood in the urine. In one previously reported case (case 1 [18]), in which there was considerable hemorrhage, in vivo complexing was suggested by the presence of equal amounts of prothrombin activity in the euglobulin precipitated from serum and plasma at a time when the prothrombin consumption was 95%. The presence of total accelerator factor activity in the serum as well as the plasma euglobulin further supported this conclusion. Although there were no hemorrhages or thrombi at the time the other previously reported case (case 2 [18]) was studied, she has since developed a hemorrhagic diathesis. The type of data presented may have predictive potentialities.

Clotting abnormalities in the presence of abnormal plasma proteins are not unknown. It is the present interpretation which is original. Shapiro, Ross and Moore [30] observed an excess of circulating anticoagulant in a case of multiple myeloma with hemorrhages, although they did not relate the hemorrhagic defect to the abnormal globulin present. Interference with the conversion of fibrinogen to fibrin has been reported by Craddock, Adams and Figueroa,[6] Uehlinger [34] and Luscher and Labhart.[25] Long et al.[23] suggested that the macroglobulin in their case acted as anti-proaccelerin (Anti Factor V) and anti-proconvertin (Anti Factor VII). Stobbe [31] suggested that the hemorrhagic diathesis in a case of multiple myeloma was due to antagonism between clotting factors and the abnormal protein. Braunsteiner, Falkner, Neumayer and Pakesch's [2] electron microscope studies in a case of macromolecular cryoglobulinemia showed that the cryoglobulin prevented pseudopod formation by the patient's and by normal platelets. Nilsson and Wenckert [27] reported a gamma globulin fraction which appeared to be acting as an anticoagulant in their case of hemophilia-like disease.

Many authors have reported clotting defects in cases of macroglobulinemia. These have included prothrombin deficiencies,[2, 8, 22, 23, 25, 31, 32, 41] reduced prothrombin conversion,[31] reduced Factor V,[8, 23, 31, 32, 41] reduced Factor VII,[8, 23, 31, 41] decreased fibrinogen,[29, 32, 36] increased antithrombin,[41] and slow or absent clot retraction.[19, 28, 32] The coexistence of such clotting problems is so well recognized that Weinreich [40] suggested that this criterion be used to differentiate macroglobulinemia from purpura hyperglobulinemica. A hemorrhagic diathesis has been reported in cases of idiopathic hyperglobulinemia,[27, 28] multiple myeloma,[13, 14, 19, 25, 30, 31] purpura hyperglobulinemica,[37] uremia [17, 21] and liver damage,[4, 5, 10] as well as in macroglobulinemia [38] and both primary and secondary cryoglobulinemia.[26, 35] Thrombotic tendencies have also been reported in cases of cryoglobulinemia [7] and cryofibrinogenemia.[16] Both hemorrhagic and thrombotic manifestations in the same patient have been reported occasionally in cases of macroglobulinemia,[29, 36] cryoglobulinemia [35] and hyperglobulinemia.[1] One case of purpura hyperglobulinemica in association with congestive heart failure has been reported.[18]

The coexistence of both bleeding and clotting tendencies in the cases presented here and in the literature is emphasized, since this phenomenon

seems to have escaped scientific explanation. Our postulated theory is the only known one which explains the occurrence of both defects at once. On the basis of the data presented here, variable reductions in prothrombin, Factor V and Factor VII as seen in a variety of clinical conditions are readily understood. Such reductions would result in hemorrhagic complications. In addition, the in vivo complexes of euglobulin with clotting factors create increased concentrations of clotting factors which would produce a thrombotic diathesis. A very low plasma level of a given clotting factor could be due to its removal by complexing with the unusual globulin in the absence of compensatory production. The plasma level of the clotting factor concerned could vary abruptly and rapidly, depending upon the production of plasma euglobulin. Hence, the plasma levels of clotting factors may be extremely variable. When these levels are low the situation would be predominantly hemorrhagic; when there are large amounts of complexed clotting factors the situation would be predominantly thrombotic. Both hemorrhages and thromboses would occur under conditions in which the measurable plasma level is low and the amount of complexed clotting factor is high.

The clinical relationship between protein abnormalities and clotting defects is well established. It is believed that the present theory explains the clotting defects in the reviewed conditions as well as in some forms of coronary occlusion.

Summary

1. Data are presented in support of a new theory to explain certain hemorrhagic and thrombotic disorders. It is suggested that under a variety of clinical conditions unusual plasma globulins are produced which complex with clotting factors, reducing the concentration of these factors and leading to hemorrhages. The clotting factor-globulin complexes result in an unstable clotting mechanism, leading to thromboses.

2. The three cases presented were selected to illustrate clinical conditions in which the offending proteins were euglobulins. The clotting factors complexed with them were chiefly Factor V and, secondarily, Factor VII and prothrombin.

3. The euglobulin-clotting factor reversible complex may be a normal mechanism for regulating the activity of Factor V and possibly other factors.

Summario in Interlingua

Es presentate datos in supporto de un nove theoria que visa a explicar certe disordines hemorrhagic e thrombotic. Es proponite que sub varie conditiones clinic inusual globulinas de plasma es producite e que illos entra in complexation con factores coagulatori, de maniera que le concentration de iste factores es reducite e que hemorrhagias es evocate. Grande concentrationes de complexos del factores coagulatori con globulina pote etiam resultar in instabilitate del mechanismo coagulatori, con le resultato que thromboses es evocate. Le evocation tanto de hemorrha-

gias como etiam de thromboses esserea a expectar quando le nivello del factores coagulatori in le circulation es relativemente basse e quando lor complexation con globulina es relativemente massive.

Es presentate tres casos que illustra conditiones clinic in que le proteinas a incriminar esseva euglobulinas. Le factores coagulatori entrante in complexation con illos esseva principalmente factor V e—secundarimente—factor VII e prothrombina.

Le patiente in caso 1 (macroglobulinemia) habeva le duple diathese de hemorrhagia e de thrombose, characterisate per purpura, hemorrhagias oral, e thrombose de un major vena intra-abdominal. Il esseva possibile demonstrar le elimination de prothrombina e factores acceleratori ab plasma native per precipitar euglobulina. Simile resultatos esseva obtenite in le re-precipitation del euglobulina ab plasma normal.

In caso 2 (etiam de macroglobulinemia), le patiente habeva un diathese hemorrhagic characterisate per sanguination nasal, hemorrhagias fundal e subconjunctival, e purpura in le extremitates inferior. Le precipitation del euglobulina resultava in un reduction, in le plasma, del nivellos de prothrombina, activitate acceleratori total, factor V, e factor VII. Le summa del concentrationes de factor V in le solution de euglobulina e in le plasma sin euglobulina amontava a 126 pro cento e esseva plus grande que le concentration mesurate in plasma native (114 procento). Quanto al 21 pro cento de factor VII que esseva presente in plasma native, solmente 7 poteva esser mesurate in le plasma sin euglobulina e 0 in le euglobulina. Post reprecipitation del euglobulina ab plasma normal, 139 pro cento de factor V esseva mesurate in le solution de euglobulina e le plasma libere de euglobulina, comparate con 88 pro cento in le plasma normal a que euglobulina habeva essite addite. Factor VII esseva reducite per 50 pro cento in le plasma libere de euglobulina e non poteva esser detegite in le solution de euglobulina. Prothrombina e summa total del factores acceleratori esseva reducite in le plasma libere de euglobulina e esseva demonstrabile in le solution de euglobulina.

Caso 3 habeva un diathese hemorrhagic-thrombotic, characterisate per purpura e sanguination renal e infarcimentos tanto splenic como etiam myocardial. Isto non esseva un caso de macroglobulinemia. Le proteina total amontava a 6,5 g pro cento, e 5,5 pro cento de illo (0,36 g pro cento) esseva precipitabile como euglobulina. Le prothrombina (sed non factor VII) esseva demonstrabile quantitativemente in le solution de euglobulina. Factor V, amontante a 112 pro cento in le plasma, non esseva reducite per precipitation del euglobulina. Tamen, le excesso de factor V mesurabile in le solution de euglobulina esseva al minus equal al excesso que habeva essite mesurate in le plasma. Es proponite que factor V esseva presente in le plasma sed que illo non esseva mesurabile quando illo esseva in complexation con le euglobulina. Factor V in le solution de euglobulina esseva liberate ab le complexo in le curso de un periodo de immagasinage. Esseva calculate que un minimo de 371 pro cento de factor V habeva essite retenite in complexation con le euglobulina.

Es proponite le these que le revertibile complexo de euglobulina con factor coagulatori es forsan un mechanismo normal pro regular le activitate de factor V e possibilemente de altere factores.

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THE WALWORTH, WISCONSIN, EPIDEMIC OF HISTOPLASMOSIS *

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Introduction

Outbreaks of acute histoplasmosis are being recognized with increasing frequency. A recent article by Lehan and Furcolow [1] summarizes reports of 38 epidemics in this country and three from foreign countries. Much useful information has been gained concerning the sources of and modes of infection with *Histoplasma capsulatum* from the study of these epidemics. The literature on histoplasmosis is adequately reviewed elsewhere [2-8] and will not be reviewed in detail in this presentation.

This report is of an epidemic of acute histoplasmosis which has some unusual features. Exposure of various types to a single source of the organisms occurred over a span of three months. Nineteen known cases of acute illness resulted. The cause of the outbreak was substantiated by the isolation of *H. capsulatum* both from the soil and from two cases. Since the date of exposure was definitely known in most cases, the incubation periods could be accurately determined. The outbreak afforded an opportunity to do serial serologic and roentgenographic studies on most of the patients and a study of the pattern of skin-test sensitivity in the community. Discussion of the exposure, incubation periods, clinical patterns and laboratory data, including cultures and complement fixation tests, x-ray findings, and the results of the skin test survey, is included in this presentation.

History of the Outbreak

The story of this outbreak revolves about the work associated with the construction of a new house on a vacant lot in the residential area of Walworth, Wisconsin. This is a community with a population of about 1,200 in the southwestern part of the State of Wisconsin.

On July 30, 1956, a ditch was dug from the water main and sewer lines under the street to the proposed foundation site. Water and sewer lines were then laid in the ditch and connected to the main lines. Two men were

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involved in the actual excavation of the ditch (table 1). One man (case 1) supervised the digging and was exposed heavily to dust from the operation. The other (case 2) ran the digging machine and closed the cab windows to keep out the dust. A third man (case 4) was occupied the whole day laying pipe and was helped part of the day by another man (case 5). A fourth (case 3) supervised the pipe-laying operation for a few hours. The city water supervisor (case 6) connected the water and sewer lines at the

TABLE 1

Walworth Histoplasmosis

Relation of Exposure to Incubation Period and Severity of Disease

Date	Case No.	Age	Hrs. of Expos.	Type of Exposure	Incubat. Per. (day)	Severity of Dis.
7–30	1	42	8	Dug ditch for water line—much dust	7 d.	Severe
	4	31	8	Laid water and sewer lines—dug in dirt	12 d.	Severe
	5	34	3	Laid water lines, helper	13 d.	Severe
	7	33	1	Observed digging—no active work	11 d.	Mod.
	2	20	8	Dug ditch for water line—in digger cab	8 d.	Mild
	3	37	2	Supervised laying of water and sewer line	13 d.	Mild
	6	46	2	Connected water and sewer at street	?	Mild
8–20	12	36	2	Placed pipe through footing forms—front	7 d.	Severe
	8	20	8	Dug footings for basement—front	12 d.	Severe
	9	33	8	Dug footings for basement—front	10 d.	Mod.
	11	19	8	Dug footings for basement—front and other walls	13 d.	Mod.
	10	46	8	Dug footings for basement—other walls	15 d.	Mild
8–23	15	58	½	Observed forms for basement	7 d.	Mod.
	16	22	½	Observed forms for basement	15 d.	Mod.
	14	48	½	Observed forms for basement	7 d.	Mild
	13	71	½	Observed forms for basement	11 d.	Mild
9–8	19	55	1	Obtained soil specimens	15 d.	Mild
11–9	17	27	8	Laid pipe in basement	14 d.	Severe
	18	27	1	Observed pipe being laid	16 d.	Mod.

main lines. Finally one other man (case 7) visited the site of work briefly to contract to cut and remove some trees remaining on the lot, but did no actual work at this time.

All of these men became ill with histoplasmosis within a period of 13 days. Case 1 became ill seven days after exposure and was the most severely ill of the cases. Cases 4 and 5 became ill after 12 and 13 days, respectively, and were both seriously ill, requiring hospitalization. Case 7 removed the trees 10 days after the initial exposure and became ill on the next day. His illness was of only moderate severity. The other three exposed had mild illnesses. Two of these had acute illness lasting from one to two weeks. However, case 6 had an illness with rather insidious onset that lasted for from four to five weeks but was not severe. A definite date for onset of illness could not be determined for him.

One additional man was present on the site this day and on several subsequent occasions without becoming ill. He later proved to have a positive skin test to histoplasmin, and on January 11, 1957, had complement fixation titers of 1:8 in the mycelial phase and 1:16 in the yeast phase.

On August 14 and 15 the foundation was excavated, using a bulldozer. The two men exposed at this time did not become ill. One subsequently proved to have a positive histoplasmin skin test and a complement fixation reaction on January 11, 1957, which was negative to the mycelial phase and positive to 1:32 in the yeast phase. The other man has not been skin tested, but on January 11, 1957, had a negative complement fixation test.

On August 20 the footings for the foundation were dug and poured. Five men were involved in this work. It was noted that three of the men (cases 8, 9 and 12) were involved specifically in digging the loose dirt in the ditch containing the water and sewer lines for the purpose of extending these lines through the footings. Two of these men (cases 8 and 12) became severely ill with histoplasmosis seven and 12 days after exposure, respectively. The other three men were not so severely ill and had their onsets 10, 13 and 15 days after exposure.

On August 23 and 24, the forms for the foundation were placed and poured. Two of the men (cases 8 and 9) who had worked at the site on August 20 did the work. Four carpenters who were repairing the roof of the house next door during the month of August (cases 13, 14, 15 and 16) casually inspected the forms for the foundation. This is their only *known* exposure to the site. These four men became ill with histoplasmosis seven, seven, 10 and 15 days after exposure. None of them was severely ill, and one actually had only a mild illness.

On September 8 a public health physician (case 19) obtained soil specimens from the site of work. She developed a mild case of histoplasmosis which began 15 days after exposure.

During the ensuing months, the pre-cut house was erected on the foundation and work continued. The work was done by those previously exposed or ill, except for two men who did plastering and interior work. Neither of these men became ill. One of them later proved to have a positive histoplasmin skin test; the status of the other is unknown.

On November 9 a shallow ditch was dug in the floor of the basement, which was not yet concreted, in order to place a drain pipe. The man who dug the ditch did not become ill. His skin test status is not known, but he is known to be a native of Kansas City, Missouri. Despite the fact that the floor of the basement was hosed with water before the pipe was laid (to hold dust down), the man laying the pipe (case 17) developed severe histoplasmosis 14 days later. One other man observing the laying of the pipe for a short period (case 18) became moderately ill 16 days after this exposure.

Shortly after this pipe was laid the floor of the basement was concreted, and no cases have been attributed to the site since.

The Site

The occurrence of these cases, all associated with the construction of the house, suggested the lot as the source of *H. capsulatum*. Specimens taken on September 8, 1956, by Dr. Margaret Hatfield were found to contain *H. capsulatum* spores.* On three subsequent occasions (October, 1956, December, 1956, and April, 1957), the site was sampled and the organism recovered each time at the Wisconsin State Laboratory of Hygiene.

Two methods were used to culture the soil:

The original method of Emmons [9] was used for the samples obtained in October, 1956. A portion of each specimen was placed in a sterile cylinder and approximately 10 times the volume of sterile physiologic saline was added. Penicillin (10,000 units) and streptomycin (10 mg.) were also added to decrease bacterial contamination. The suspension was then mixed vigorously and allowed to stand for about 25 minutes. A 10 ml. sample of the supernatant was withdrawn and 1 ml. was injected intraperitoneally into each of four mice. Mice were killed at two and four weeks' time and cultures were made from their livers and spleens. They were placed on blood agar and Sabouraud's agar for incubation at room temperature, and on blood agar and Francis' cystine agar for incubation at 37° C. Growth began on about the tenth day if positive, but the plates were kept for four weeks before they were discarded as negative. The yeast phase colonies were changed to mycelial by incubating those that had grown at room temperature at 37° C., and vice versa.

The subsequent sets of specimens were cultured by the method suggested by Larsh et al.[10] One milliliter of each soil specimen was placed in a sterile container, and physiologic saline solution was added to make a total of 10 ml. Streptomycin and penicillin were added as before. The soil and water were mixed, and 1 ml. of the mixture was injected intraperitoneally into each of eight mice before the suspension could settle. The mice were autopsied at four and eight weeks, and their livers and spleens were cultured as above. Growth again appeared in about 10 to 12 days, but the cultures were saved for four weeks. The colonies were changed to the mycelial phase as above. The organism was recovered from one mouse killed at four weeks and from two killed at eight weeks in the two groups of mice done.

On two occasions the soil samples were also tested to determine their pH. The positive samples had a pH of 6.0 and 6.55. Negative samples from the rear of the lot all had a pH of 6.9 or above. Only the soil on the front of the lot had a pH below 7. An acid pH has been a consistent characteristic of soils from which *H. capsulatum* have been grown.[11-13]

There was no knowledge of the existence of a building on the lot at any time. Neither fowl nor animals had ever been kept or housed upon the lot. It is fairly well established that during the summer of 1946 the dense trees on the front of the lot were a roosting place for starlings. At that time the ground and sidewalk on the front of the lot were covered with droppings.

* This isolation was done at the Kansas City Field Station, U. S. Public Health Service, DHEW.

At the time of the outbreak (1956) there was no evidence of bird droppings on the lot or sidewalk.

General Clinical Pattern of Illness

The incubation period could definitely be determined in 18 of the cases. The other case had an insidious onset, and a definite incubation period could not be stated. The range of the incubation period was from seven to 16 days, with a mean of 11.3 days (table 1). Incubation periods were not related to the age of the patient, amount of exposure or subsequent severity of disease.

The onset of illness was characterized by the acute onset of fever, malaise, weakness and headache in 12 of the cases. Chills and sweating were common accompanying presenting symptoms. In five additional cases there seemed to be a prodromal period marked by malaise and weakness varying from two days to about two weeks before onset of fever and other symptoms. In four of these five the onset of malaise was so marked that the day of onset could readily be recalled. In two additional cases the whole course of the disease was marked by malaise, weakness, muscular aches and cough, but without known fever or other symptoms.

Fever was known to be present in all but two cases. In these two there was no subjective fever, and their temperatures were not taken. The fever varied from 100° F. to 104° F., and was usually 102° F. or 103° F. Headache was also frequent, and in a few patients was severe. Shaking chills were present in 15 cases, and profuse diaphoresis was present in 12. This diaphoresis seemed remarkable for the amount of fever present. Cough was present in all but one patient. It was not, however, a prominent symptom, and often was merely a few days of hacking cough productive of small amounts of sputum. In a few patients the cough was severe. Pleuritic pain was present at some time during the course of illness in 11 cases. This varied from pain so severe that cough was suppressed in one patient, to a week of mild pleurisy during convalescence in another. In addition, six cases noted pain in the anterior chest which was unrelated to respiration. This was not usually severe, and lasted about one to two weeks during the acute illness. Dyspnea to varying degrees was present in eight patients. Weakness was a prominent part of the clinical picture and occurred in 16 cases. This often persisted for as long as a month after the patient was otherwise well, and was disturbing to those who were accustomed to doing rather heavy work.

The physical findings in these patients were for the most part minimal. Fifteen of the cases were examined at some time during their acute illness. Eleven of these had chest findings consisting of only a few scattered crepitant râles. No local mucous membrane lesions were noted, although three patients complained of slight sore throat, and one had conjunctivitis. Lymphadenopathy was not present to a significant degree in these patients.

A pleural-pericardial friction rub was found in one patient. The chest findings would not have led one to suspect a severe pneumonitis.

Three patients had palpable livers that were slightly tender. The spleen was not palpable in any of the patients, but it appeared to be enlarged on an x-ray in one patient.

X-Ray Patterns

The details of the x-ray findings on these cases will be described elsewhere.[14] X-ray examination of the chest was obtained on 13 patients during the acute illness; 10 showed parenchymal lesions.

The parenchymal lesions were diffuse nodules in eight cases, diffuse miliary nodules in two cases, and diffuse mottling bilaterally in one case. Four of the 10 with parenchymal lesions also had hilar lymph node enlargement. Two additional patients showed only hilar lymph node enlargement. Four of these six cases showed bilateral hilar node involvement, and two showed enlargement of only the right hilar nodes. The chest x-ray of one case was read as "normal."

The first impression of the radiologist in two cases was that of metastatic carcinoma. In one case miliary tuberculosis and in another case congestive failure were the initial impressions. Follow-up x-rays one year after illness did not reveal the development of calcification.

These findings reëmphasize the fact that the appearance of the chest x-ray during the acute phase of the disease is not pathognomonic for histoplasmosis. However, if the diagnosis is suspected on other grounds the appearance of the x-ray may strongly support it.[5, 6, 15] It must be remembered that a "normal" chest x-ray should not discourage the diagnosis of histoplasmosis.

Laboratory Findings

The leukocyte count in eight cases varied from 6,600 to 18,300, with a median of 10,000. The differential counts showed 60 to 75% polymorphs. The hemoglobin varied from 12 gm. to 15.8 gm. The sedimentation rate (Wintrobe method) was elevated in all cases where it was performed. It varied from 18 to 48, with a median of 30. Urine examination was normal except for minimal albuminuria in two seriously ill patients.

The histoplasmin skin test was positive on the 18 of this group that had been tested. These tests were done from three days to five months after onset with either commercial antigen * or antigen supplied by the State Laboratory of Hygiene. The remaining case has not been tested but has had positive complement fixation titers. His skin test would be expected to be positive.

Complement fixation tests were performed at the Wisconsin State Laboratory of Hygiene. The following were the methods used:

* Histoplasmin—Parke-Davis Co., Eli Lilly Co.

The histoplasmin was made according to the procedure of Salvin and Hottle [16] using stock cultures of *H. capsulatum* which had been maintained on Sabouraud's agar at room temperature. The flasks of synthetic medium were seeded and left at room temperature for eight to 10 weeks. During this period there was good mycelial growth, and the pH shifted from 7.0 to approximately 8.5. After sterilization by Zeitz filtration, the finished product was stored at 4° C. until needed. For

TABLE 2

Histoplasmin Complement Fixation Tests on 11 Selected Patients, Walworth County, 1956

(Values are Reciprocals of Titer)

Case No.		Weeks After Onset																
		1	2	3	4	5	6–7	8–9	10–11	12–13	14–15	16–17	18–21	22–25	26–33	34–41	42–49	50–57
1	M*	—	—	—	—	—	16	—	16	0	0	8	—	—	—	—	—	8
	Y†	—	—	—	—	—	64	—	64	64	64	64	—	—	—	—	—	8
4	M	—	—	0	—	32	16	32	—	—	32	—	—	—	8	4	—	—
	Y	—	—	0	—	32	32	64	—	—	64	—	—	—	32	16	—	—
5	M	—	—	0	—	32	—	64	—	—	64	—	—	16	—	—	—	—
	Y	—	—	64	—	256	—	256	—	—	256	—	—	128	—	—	—	—
7	M	—	—	—	4	—	—	8	—	—	—	—	—	—	4	4	—	—
	Y	—	—	—	32	—	—	32	—	—	—	—	—	—	8	4	—	—
8	M	—	32	128	128	128	—	—	32	—	—	—	16	—	8	0	4	—
	Y	—	32	128	128	128	—	—	64	—	—	—	64	—	16	0	8	—
9	M	—	—	—	—	—	16	8	16	—	—	—	16	—	—	—	—	—
	Y	—	—	—	—	—	128	64	64	—	—	—	64	—	—	—	—	—
10	M	—	0	—	32	—	—	—	—	—	—	—	64	—	—	16	—	—
	Y	—	8	—	32	—	—	—	—	—	—	—	32	—	—	16	—	—
11	M	—	64	64	64	—	—	—	—	—	—	—	32	—	—	8	—	—
	Y	—	64	64	64	—	—	—	—	—	—	—	64	—	—	16	—	—
12	M	—	0	—	16	32	32	—	16	—	—	—	32	—	4	4	0	—
	Y	—	0	—	64	64	64	—	32	—	—	—	64	—	16	16	0	—
14	M	—	8	—	—	8	—	—	—	—	—	—	16	—	—	—	—	—
	Y	—	16	—	—	64	—	—	—	—	—	—	32	—	—	—	—	—
15	M	—	32	—	—	32	—	—	—	—	—	—	32	—	—	0	—	—
	Y	—	64	—	—	64	—	—	—	—	—	—	64	—	—	8	—	—

* M—Mycelial phase of the organism used only in complement fixation test.
† Y—Whole organism in yeast phase used in complement fixation test.

the yeast phase antigen, the yeast culture (Indiana silo strain from Dr. Loosli's laboratory) was grown on Francis' cystine blood agar in Roux bottles for eight to 10 days. The growth was washed off with Veronal buffer containing 0.5% formalin. After 24 hours the yeast suspension was centrifuged and the sediment washed three times with Veronal buffer. This heavy suspension of yeast cells is stored at 4° C. until needed. Merthiolate at a concentration of 1:10,000 is added to both antigens.

Antigen concentrations for the complement fixation test were determined from

block titrations of varying dilutions of antigens against immune rabbit serum as well as known positive human serums of low and high titers. The dilutions of antigens which show the greatest fixation with the various serums are the dilutions chosen for testing unknown serums. In this study a 1:6 dilution of histoplasmin and a 1% suspension of yeast cells were used.

Veronal buffer was used throughout in the complement fixation test as diluent. After inactivation at 56° C. for half an hour, serums were diluted twofold beginning with a 1:4 dilution. Two exact units each of complement and hemolysin were used with overnight incubation at 4° C. The final volume of the test was 1.5 ml., and each test was read for complete fixation. Only the highest dilution showing a 4 plus reaction was reported.

The results of the complement fixation test varied considerably for the 11 cases where three or more titers were determined (table 2). One patient (case 12) had a negative test during the second week of illness, and another (case 3) was negative during the third week of illness. On the other hand, two patients (cases 11 and 15) had reached their peak titers by the time they were tested during the second week of illness. Allowing for a one dilution variation, by the fourth or fifth week following onset, we found that all those who had been tested had reached a peak titer. By the fifth month after illness the titers of seven of the cases were still 1:32 or better to the yeast-phase antigen; after this, they appeared to drop off slowly. However, by the tenth to twelfth month following onset most of the patients tested were still positive in a low dilution. The amount of rise in titer was not necessarily related to the severity of the disease, in that some of those only moderately ill had titers as high as those who were severely ill. However, patients who were not severely ill did not have complement fixation titers above 1:64. The peak titer reached was 1:256 in one patient (case 5).

Both the mycelial and the yeast phases of *H. capsulatum* were used for the complement fixation tests. The yeast titer was usually higher than the mycelial titer. However, with one possible exception (case 14), there would have been no difference between the two as supporting evidence for the diagnosis. The results are somewhat different if only those cases where it was not possible to obtain more than one or two specimens are considered. These cases have not been included in table 2. Out of these eight cases, seven had single titers of more than 1:8 using the yeast antigen, as opposed to only two with the mycelial antigen. If the titer considered positive is raised to more than 1:16, the number of cases is reduced to four for the yeast and one for the mycelial. Five of these eight cases had two tests. Four of these showed a change of two dilutions or more with the mycelial antigen, whereas only two showed significant change with the yeast antigen.

One must be cautious about generalizing on the results of one laboratory in that titers may vary in other laboratories where different isolates of *H. capsulatum* are used.[17-20] It would appear from our small series and the experience of Allan [21] that use of both yeast and mycelial phases for the complement fixation test is of value.

FIG. 1. Photomicrograph of lymph node removed from case 8, showing encapsulated *H. capsulatum* spores (hematoxylin eosin).

FIG. 2. Photomicrograph of tuberculated spores found in culture of lymph node from case 8.

Complement fixation tests for blastomycosis * were done on two patients during the fourth and fifth weeks of illness. The titers were 1:32 in each instance. The significance of this will be discussed later.

Cultural proof of infection with *H. capsulatum* is highly desirable. Attempts were made in three patients to culture the organism from the sputum and blood but were not successful. Bone marrow examination on four cases did not reveal the organism by either histologic or cultural means. Scalene lymph node biopsies and cultures were done on two patients (cases 8 and 12). The organism was apparent on histologic examination of a node from one of them (figure 1). The nodes were emulsified and placed on Sabouraud's and blood agar media within 15 minutes after removal. Growth took two weeks. *H. capsulatum* was cultured from the nodes of both patients (figure 2).

Treatment of Cases

Many of the patients were given a variety of antibiotics when first seen by their physicians, with no appreciable effect. Reports of the possible efficacy of amphotericin B in the treatment of histoplasmosis [22] led to the treatment of three patients with this drug. All three received 3.2 gm. by mouth per day for three months. The efficacy of the treatment in these patients is difficult to evaluate. Treatment was begun during early convalescence in two patients (cases 1 and 12). No acceleration in the rate of recovery was noted. The remaining patient (case 8) began taking the drug 10 days after onset. Three days later his fever fell and he began to recover. Any relation of this improvement to the administration of the drug would be highly speculative. Lehan et al.[22] have now had considerable experience with amphotericin B in treating histoplasmosis. It is pointed out that poor absorption of the drug from the gastrointestinal tract makes this route of administration open to question. Results have been encouraging in acute disseminated and cavitary cases when the drug is used intravenously.

Epidemiologic Data

The site of this outbreak is of particular interest. In a recent summary of the known epidemics of histoplasmosis, Lehan and Furcolow [1] pointed out that 23 of the 41 epidemics considered (56%) were associated with exposure to bird or bat excreta. An additional 13 (32%) were associated with visits to a farm cellar, barn or cave.

The occurrence of an outbreak on an open lot with no evidence of bird droppings present is unusual. It is worth while to keep this in mind when asking a patient about a possible source of infection with *H. capsulatum*. Even though old enclosures with evidence of bird excreta are characteristic

* These tests were done by the Communicable Disease Diagnostic Laboratory, U. S. Public Health Service, Chamblee, Georgia.

of such sources, a more innocuous exposure to soil or rotting wood can well be involved.

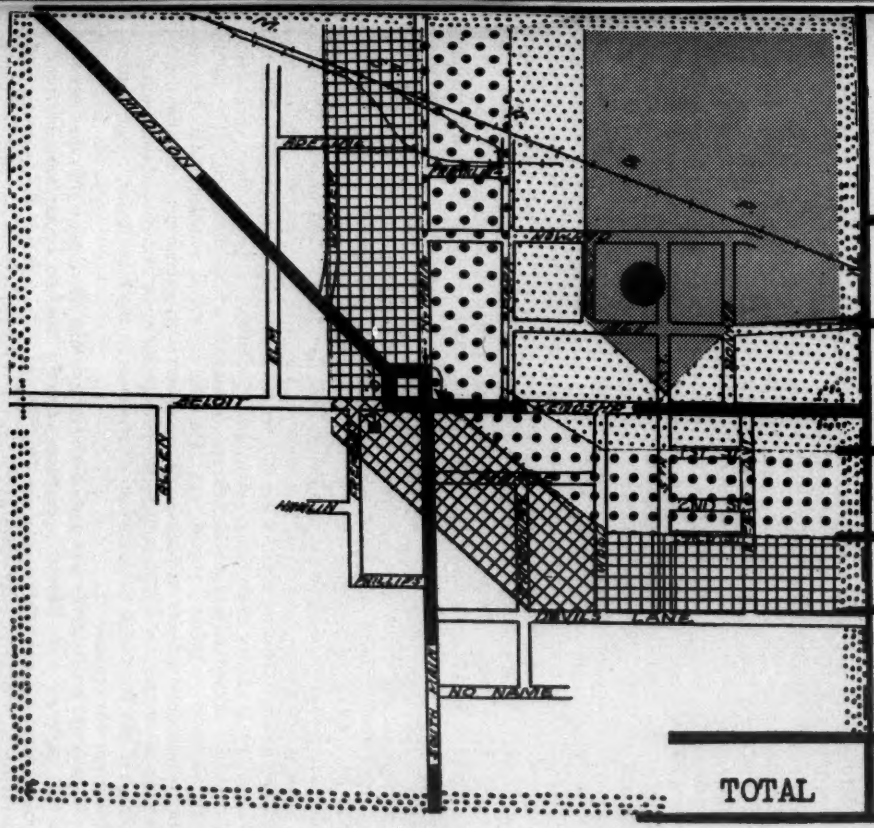
The site involved in this outbreak was an ordinary-looking lot on a residential street of this village. The source of *H. capsulatum* in the soil remains speculative. The fact that the soil on the front of the lot was acid, whereas the soil on the rear of the lot had pH of 7.0 or greater, suggests that at some time a change in the soil composition occurred in certain areas of the lot. The presence of shade trees on the lot served to protect the organism from the sun. It is most likely that the organism had been present for a long period of time at the site but did not disseminate until the soil was disturbed. The fact that positive cultures were obtained from frozen soil in December and again in the spring demonstrates the ability of this organism to survive through winter.

The occurrence of an outbreak of histoplasmosis in a nonendemic area prompted an inquiry into the rate of skin test reaction in the village and its environs. A testing program was carried out in the community in January and February, 1957, and involved the children in the school and adults from the community and surrounding rural area. The details of this survey will be reported elsewhere.[24]

Manos et al.[7] and Edwards,[25] in a nation-wide study done by the U. S. Public Health Service over a period of several years, found a reactor rate of 8.2% for the 17- to 21-year age group among student nurses, college students, and naval recruits from Walworth County and four other surrounding counties. Our testing revealed that 11.4% of 492 tested who had lived 80% or more of their lives within Walworth County were skin-test positive (all ages included). When the residents of Walworth Village were separated from those who lived in the surrounding rural area, it was found that 15.7% of the village residents and only 4.3% of the rural residents were skin-test positive. Others [27-30, 32] have found that the rural reactor rate is ordinarily equal to or higher than the urban, quite the reverse of the situation in the Walworth vicinity.

This led us to analyze our data with respect to the site of the outbreak. The village was divided geographically into zones of approximately one block in width, using the site of the outbreak as a center, as shown in figure 3. Including all persons tested, we find that within one block of the site of the outbreak 40.5% of those tested were positive. In the next zone only 23.8% were positive. In successive zones, 12.5, 9.7 and 20.0% were found to be positive reactors. The total per cent positive reactors in this case is 17.4, since all tested are included regardless of length of residence in the county.

The problem presented to the community by this potential source of infection is apparent. The skin-test survey suggests that this site did indeed infect many in the community. It is not possible to determine whether these reactions represent recent or old infections. Thirty-three of 112 positive



NO. POS.	NO. TEST.	% POS.
17	42	40.5
16	67	23.8
15	120	12.5
14	145	9.7
23	115	20.0
TOTAL 85	489	17.4

FIG. 3. Walworth Village, geographic distribution of histoplasmin reactions. Map indicating concentric zones approximately one block in width using known source of *H. capsulatum* as center and the incidence of skin-test-positive individuals in each zone. ● indicates source of infection.

histoplasmin reactors had a complement fixation test with a titer of 1:8 or over in March and April, 1957. This would suggest that the site was a source of recent acute infections which were either inapparent or undiagnosed. The economic loss to the workers as well as to the owner of the lot was substantial. Protection of individuals subsequently using this site is a problem which has no clear-cut answer.

Case Reports

Case 1. The patient, a 42 year old sewer contractor, had been in good health until August 6, 1956, when he developed weakness and malaise. This continued for one week and then he began to notice vague pains in his anterior chest. On August 13, 1956, he suddenly developed a hard shaking chill, which was followed by a temperature of 104° F. (oral). He was seen by his physician, who gave him 400,000 units of procaine penicillin. The next day (six days before admission to St. Joseph's Hospital) he was admitted to his local hospital because of the persistence of his fever and a severe, dry, hacking cough. Laboratory findings on August 15, 1956, were as follows: white blood cells, 10,150; hemoglobin, 15.6; hematocrit, 52; sedimentation rate, 32 mm./hr. The penicillin was continued in a dosage of 400,000 units given daily, and tetracycline, 250 mg. by mouth four times a day, was added to his therapy. In spite of this he continued to have a high spiking fever each day and a hard, racking cough. After 48 hours of therapy with penicillin and tetracycline the antibiotics were changed to chloramphenicol, 1 gm. intravenously stat, and 0.5 gm. by mouth four times a day, and erythromycin, 1 gm. intravenously stat and 1 gm. intravenously daily. When the patient continued to be acutely ill in spite of 48 hours of chloramphenicol and erythromycin therapy he was transferred to Milwaukee. A blood culture drawn during his fifth day of hospitalization grew *Pseudomonas aeruginosa*. The pertinent physical findings on admission to St. Joseph's Hospital on August 20, 1956, were: temperature, 103° F.; pulse, 100; respiration, 18; blood pressure, 128/70 mm. of Hg. The patient appeared to be acutely ill. He had a dry, nonproductive cough. There was a mild conjunctivitis bilaterally, but there was no significant lymphadenopathy. The chest examination revealed scattered crepitant râles, but no evidence of consolidation was thought to be present. The heart was normal. The spleen was not palpable. The liver was enlarged 4 cm. below the costal margin, and was tender. There were no other pertinent findings.

Laboratory findings on admission were as follows: hemoglobin, 13.5 gm.; white blood cells, 6,000; differential count: 75% polymorphonuclears, 21% lymphocytes and 4% monocytes. Sedimentation rate, 20 mm. per hour. Non protein nitrogen, 33.5 mg.%; chlorides, 104 mEq./L.; sodium, 134 mEq./L.; cephalin cholesterol, negative; serum bilirubin, total, 2 mg.%; serum protein, 5.9 gm.% (3.75 albumin, 2.15 globulin). Urine: specific gravity, 1.022; albumin, 2 plus; sugar, negative; microscopic: occasional red blood cell and occasional white blood cell. The chest x-ray was read as follows (figure 4): "Multiple somewhat rounded fairly discrete areas of increased density in both lungs associated with enlargement of hilar nodes which in the absence of a clinical picture of neoplasm most likely represents multiple pulmonary abscesses with inflammatory enlargement of the hilar nodes." An electrocardiogram was normal.

Course: Because of the positive blood culture, lack of response to other agents, and the patient's poor clinical appearance, therapy for the bacteremia due to *P. aeruginosa* was begun with oxytetracycline, 0.5 gm. intravenously twice a day, and polymyxin B, 50 mg. intravenously daily (in 1 L. of 5% dextrose in water). There appeared to be a prompt clinical response to the above therapy, and it was continued

for several days. Neomycin aerosol therapy was added to increase the antimicrobial pressure against what were considered to be multiple lung abscesses. Forty-eight hours after admission the patient's wife volunteered the additional information that six of her husband's co-workers were in another hospital, all with "severe pneumonia." This immediately suggested to us the possibility of histoplasmosis, and a skin test was put on the patient. It was markedly positive within 24 hours. Blood was drawn for complement fixation studies at this time, and titers of 1:16 in the mycelial and 1:64 in the yeast phase were found. Bone marrow examination was normal,

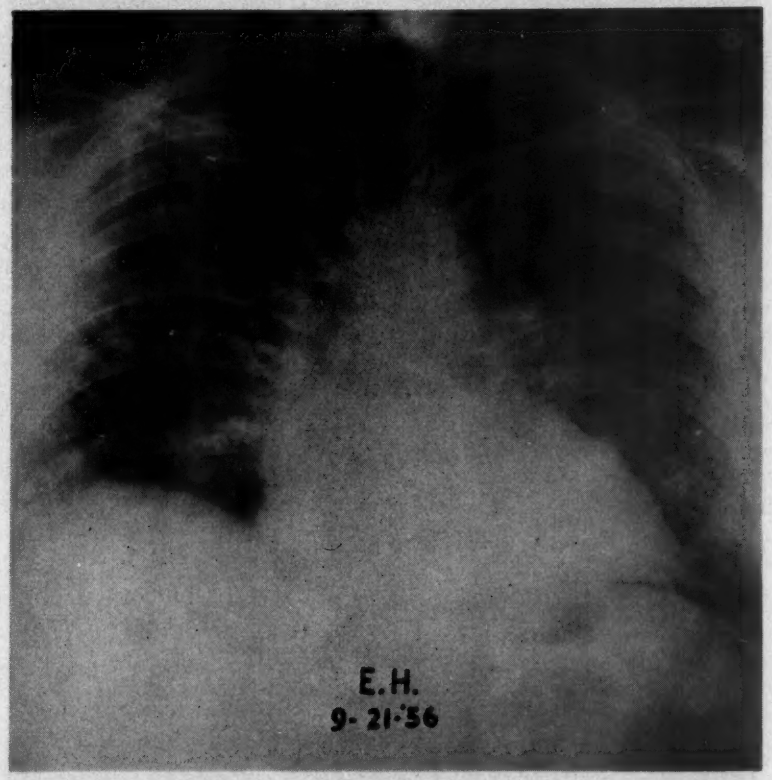


FIG. 4. Chest x-ray of case 1 during acute illness, showing nodular densities in both lung fields and enlargement of hilar lymph nodes.

and cultures of the bone marrow and sputum were negative for histoplasmosis. *P. aeruginosa,* however, was cultured from the sputum initially. The antibiotics were discontinued after four days. The fever diminished daily, and after six days in the hospital the patient was afebrile. At this time his x-ray had shown some clearing. He felt much better but still complained of weakness and shortness of breath. Pseudomonas was no longer cultured from the sputum. The referring physician was then informed of our opinion that the patient and his coworkers were suffering from histoplasmosis, and the diagnosis was confirmed in the other workers. On the ninth hospital day, therapy with amphotericin B, 800 mg. by mouth four times a day, was

begun and was continued for three months. When the patient felt better, careful questioning revealed that on July 30, seven days before he first felt ill, he had dug the sewer ditch for the house in Walworth, Wisconsin, which was later shown to be the source of the outbreak. He had sat on the arm of his ditching machine and remembered distinctly that it was a dusty day. The entire exposure on that day had been eight hours.

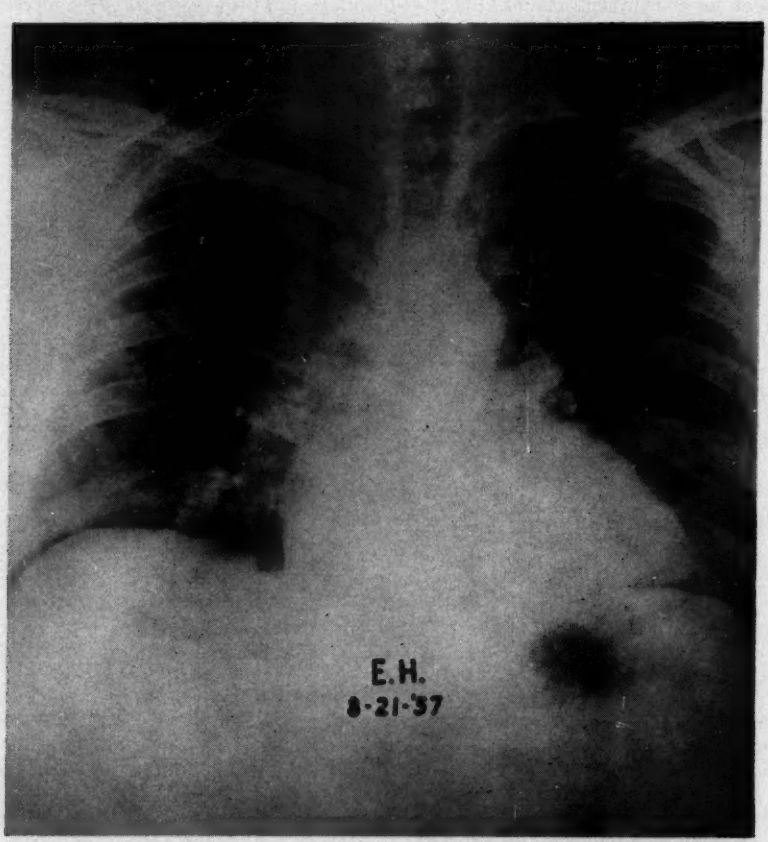


FIG. 5. Repeat chest x-ray of case 1 taken about one year after onset. Marked clearing is present, but densities are still apparent in both lung fields and the hilar nodes are still enlarged.

The patient was discharged for follow-up as an out-patient after 16 days in the hospital. At that time he still felt short of breath, nervous, and "not himself." His x-ray had shown further resolution of the pneumonic process. His vital capacity was 1,300 c.c. after the first week of hospitalization, and 3200 c.c. just before discharge from the hospital. Sedimentation rate at this time had risen from 20 mm. per hour to 38 mm. per hour.

Our opinion at the time of discharge was that the patient probably did have, in addition to histoplasmosis, a secondary *P. aeruginosa* bacteremia. The epidemi-

ologic story that evolved was so striking, however, that the diagnosis of histoplasmosis was also a certainty, and this led us to the complete study we are now reporting.

Follow-up: The patient felt chronically ill until about May, 1957, when he began to feel "his old self." Amphotericin B, 800 mg. per day, was given for a total of three months. Interval x-rays have shown continual improvement. The x-ray taken one year after onset (figure 5) is still not normal but is vastly improved. Laboratory studies done during the year revealed normal sedimentation rate, normal liver function studies and normal serum proteins. Complement fixation studies are shown in table 2. The physical examination one year after onset of the illness was normal, and the patient states that he feels perfectly well.

Comment: The initial case in the epidemic apparently developed in addition a secondary infection with *P. aeruginosa.* The patient has steadily improved after six months of easy fatigability and generalized malaise. At present he is actively working without complaint. Calcification has not as yet appeared in his lungs. The role of amphotericin B given orally in changing the course of his disease remains conjectural.

Case 2. The patient, a 20 year old white male, became ill on August 7, 1956, with headache, malaise, chest pain and cough. He did not feel feverish. On July 30, 1956, he assisted case 1 for eight hours in digging the ditch to lay sewer and water lines at the site of the outbreak. The symptoms were not severe, but prevented him from working for 10 days and persisted for about three weeks. On August 24, 1956, when the patient first saw his physician, the symptoms were subsiding. At this time physical examination revealed no abnormality. Chest x-ray revealed enlarged hilar lymph nodes but no other abnormality. The histoplasmosis skin test was said to be positive. Repeat skin test on January 23, 1957, was positive. Skin tests with tuberculin and blastomycin were negative. Complement fixation tests on October 3, 1956, revealed a mycelial titer of 1:32 and a yeast titer of 1:64. Repeat test on January 11, 1957, revealed a mycelial titer of 1:128 and a yeast titer of 1:32. The patient recovered from his illness without incident and has had no sequelae.

Comment: Although this patient worked with case 1, it was noted that he had closed the cabin of the digger, partially protecting himself from the dust, whereas case 1 worked in the open.

Case 3. The patient, a 37 year old white male, became ill on August 12, 1956, with malaise, weakness, cough productive of a scant greenish sputum, and pain in the anterior chest unrelated to the cough. On July 30, 1956, he had supervised the laying of pipe at the site of the outbreak. He had worked about two hours at the site. The illness was mild and only partially disabled him for about 10 days. He felt well after two weeks and was not seen by a physician until September 11, 1956. At this time physical examination revealed no abnormalities, and chest x-ray was normal. On March 20, 1957, and April 29, 1957, the complement fixation tests with both mycelial and yeast phase were 1:8.

Comment: The diagnosis was based on a definite exposure, with an acute illness following within the incubation period. A complement fixation test done seven months later being positive at a low titer is suggestive supporting evidence.

Case 4. The patient, a 31 year old white male, became ill on August 11, 1956, with fever to 103° F., chills, malaise, headache, myalgia, profuse sweating, weakness

and sore throat. On July 30, 1956, he had spent eight hours laying pipe at the site of the outbreak. He became severely ill within a day and was seen by his physician. After three days of therapy with erythromycin no improvement had occurred, and treatment with penicillin was begun. On August 20 the patient developed a slight cough and pleuritic chest pain, and was admitted to the hospital. Physical examination at this time revealed an acutely ill man with no other remarkable physical findings. Examination of the chest and abdomen revealed no abnormalities. Chest x-ray revealed diffuse nodular densities bilaterally. Terramycin therapy was begun and the penicillin continued. The next day the white blood cell count was 8,600, with 60% polymorphonuclears and 38% lymphocytes. The hemoglobin was 12.6 gm. Bacterial examination of the sputum was negative on August 25 and August 26, 1956. On August 28, 1956, the histoplasmin skin test was noted to be positive, and the complement fixation tests with both the yeast and the mycelial phases were negative. On September 10 the complement fixation test was positive at 1:32 titer in both mycelial and yeast phases (table 2). The white blood cell count on this day was 6,600; hemoglobin, 13 gm.; sedimentation rate, 19 mm./hr.

On August 31 the patient was discharged somewhat improved. He continued to have severe weakness and malaise. On September 10 the white blood cell count was 6,600; hemoglobin, 13 gm.; sedimentation rate, 19 mm./hr. The chest x-ray was unchanged. By the end of September the chest x-ray showed some clearing and the patient's symptoms were subsiding. By early November he was well enough to return to work full-time. He is completely recovered at present.

Case 5. The patient, a 34 year old white male, had been in good health until he became ill on August 12, 1956, with fever to 103° F., chills, weakness and headache. On July 30, 1956, he had assisted for three hours in the pipe laying at the site of the outbreak. The next day he developed moderate dyspnea and a cough productive of a small amount of brownish sputum. Physical examination on the second day revealed a few crepitant râles at the right lung base but no other abnormal findings. The symptoms persisted with symptomatic treatment and antibiotics. When he showed no improvement he was hospitalized on August 27, 1956. At this time the white blood cell count was 18,300; hemoglobin, 13.4 gm.; sedimentation rate, 48 mm./hr. Chest x-ray showed enlarged hilar lymph nodes and extensive bilateral nodular infiltrates. On August 29, 1956, the histoplasmin skin test was read as positive, and the complement fixation was negative for the mycelial phase and positive at 1:64 dilution for the yeast phase. The patient was discharged from the hospital on August 31, 1956, and a convalescent period of gradual recovery marked by weakness and dyspnea followed. He was able to return to work by the end of October. In early October his complement fixation titer rose to a peak of 1:128 in the mycelial phase and 1:256 in the yeast phase. On January 28, 1957, complement fixation titers were 1:16 in the mycelial phase and 1:128 in the yeast phase (table 2). By this time the patient felt completely well.

Case 6. The patient, a 46 year old white male, on July 30, 1956, spent two to three hours inspecting the sewer and water lines at the site of the outbreak, and joined them into the city main. He had gradually increasing malaise and weakness during the last two weeks of August, 1956. He first noted fever up to 102° F. on August 31, 1956, together with chills and headache. These symptoms persisted but did not become severe until September 4, 1956, when profuse sweating and a hacking cough appeared, with increase in the previous symptoms. On September 8, 1956, the patient sought medical attention. Physical examination at this time revealed no abnormalities, and chest x-ray revealed hilar node enlargement but was not otherwise remarkable. On September 10, 1956, repeat examination revealed that the liver was enlarged 8 cm. below the right costal margin. No other abnormalities were noted. On this date the skin test with histoplasmin was positive (12 by 8 mm. of induration),

and the tuberculin skin test was read as negative. Complement fixation test revealed a titer of 1:32 with the yeast phase. On September 14, 1956, icterus index was 3.0 and total protein was 6.7, with an A/G ratio of 1:32. On September 17, 1956, the patient returned to work part-time, as his symptoms had subsided. On September 29, 1956, the titers of the complement fixation tests were 1:8 in the mycelial phase and 1:64 in the yeast phase. On January 11, 1957, the yeast phase was negative and the mycelial phase 1:32. At this time he had recovered completely.

Comment: This patient's illness was distinguished by its insidious onset. It is difficult to evaluate the palpable liver. He failed to return for follow-up examination, so the convalescent status of the liver is not known.

Case 7. The patient, a 33 year old tree trimmer, had been in good health until August 10, 1956, when he developed malaise, fever, chills, headache and muscle aches. On July 30, 1956, he had visited the epidemic source for one-half to one hour and had cut down and removed three trees from the lot on the day prior to onset. His illness continued, and on August 15, 1956, he consulted his family physician. Physical examination at this time was normal except for scattered fine râles in both lungs. Treatment was begun with penicillin. The following day he developed cough and pleuritic pain. On August 18, 1956, chest x-ray revealed multiple round densities bilaterally. The first interpretation of the x-ray was "possible metastatic carcinoma." On August 24, 1956, the histoplasmin skin test was positive, and on September 6, 1956, the complement fixation with the mycelial antigen was 1:4 and with the yeast antigen was 1:32. His sedimentation rate at this time was 18 mm./hr. On September 19, 1956, his white blood cell count was 7,800, and hemoglobin, 12 gm.

The patient lost about 10 pounds during his acute illness. He continued to have weakness and cough, but returned to work about October 1, 1956. He did not feel normal until November. His chest x-ray showed gradual improvement, so that by March 2, 1957, it was read as normal. The complement fixation test with both antigens was 1:4 on April 29, 1957 (table 2). The patient gradually recovered and has had no residual difficulty.

Comment: This man did no work on the day of exposure but merely observed the work for a brief period. Despite this he had moderate to severe illness, characterized by a long period of weakness following the acute phase.

Case 8. The patient, a 20 year old carpenter's apprentice, on August 20 helped prepare footings in the basement of the house in Walworth, Wisconsin. Two weeks later he developed malaise, chilly sensations, generalized body aches and a dry, nonproductive cough. With these symptoms he continued to work for four days and then saw his physician who, knowing of the epidemic of histoplasmosis, hospitalized him and found pulmonary lesions on x-ray as well as a positive skin test for histoplasmosis. For the next 10 days the patient remained in a local hospital, where he ran a daily spiking fever. On August 10, laboratory results were: white blood cells, 7,700; hemoglobin, 13.4; hematocrit, 44; sedimentation rate, 40. At this time his temperature rose to 104° F. and he developed pleurisy and dyspnea. He was transferred to St. Joseph's Hospital in Milwaukee on September 15, 1956. There was no other significant past medical history. Physical examination on admission revealed the following: temperature, 102° F.; pulse, 80; respirations, 16 and shallow; blood pressure, 110/70 mm. of Hg. The patient appeared to be very dry and apprehensive. There were fine crepitant râles at the left base of his lung fields. A pleural-peri-

cardial friction rub was clearly heard. The spleen was not palpable, but the liver was enlarged and slightly tender. There were no other significant physical findings.

Laboratory studies were as follows: hemoglobin, 14 gm.; leukocyte count, 10,300, with 77% polymorphonuclears, 18% lymphocytes and 5% monocytes; sedimentation rate, 36 mm. Urinalysis: specific gravity, 1:027; protein, 1 plus; no sugar or cellular elements were seen. The complement fixation test for histoplasmosis was 1:32

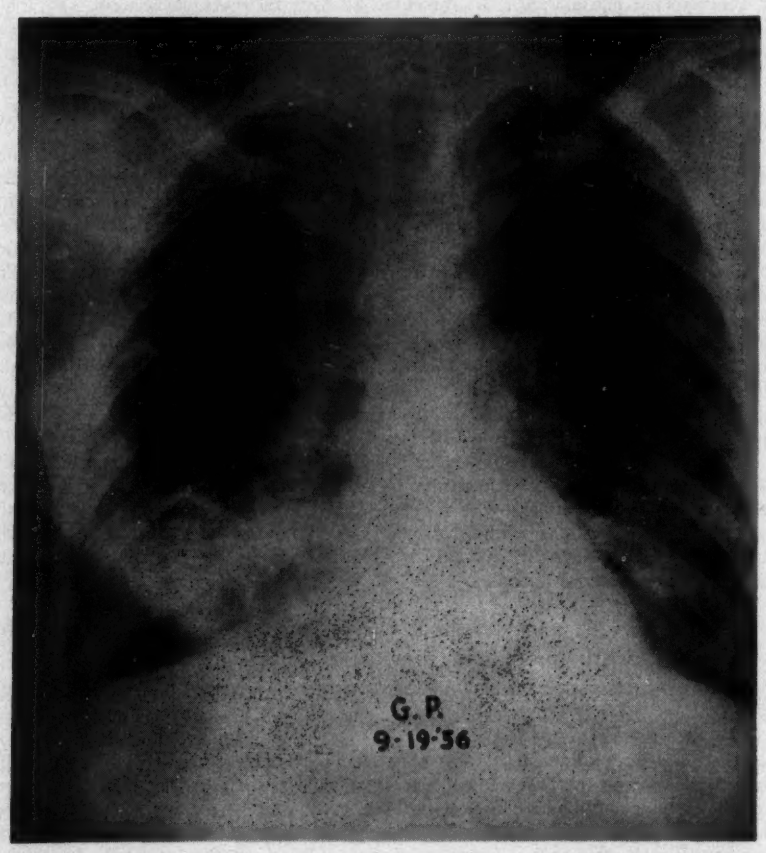


FIG. 6. Chest x-ray of case 8 during the acute illness, showing extensive bilateral densities.

(mycelial and yeast phase) on September 12, and by September 18 was 1:128 for both antigens (table 2). Complement fixation test for blastomycosis was 1:32 on October 2. Multiple blood cultures and sputum cultures revealed no pathogenic bacteria or fungi. Bone marrow examination was normal, and culture of bone marrow revealed no fungi. A rat and a guinea pig were injected with the bone marrow, and when sacrificed in one month showed no infection with histoplasmosis. Cephalin cholesterol was 4 plus; bromsulfalein, 16% dye retained after 30 minutes; nonprotein nitrogen, 28 mg.%; serum protein, 4.05 albumin and 3.25 globulin. Vital capacity was 3,450 c.c.

Chest x-ray was read as follows: "Extensive bilateral pulmonary changes. The major change was on the right. The scattered densities are compatible with extensive bronchopneumonia (figure 6)." Flat plate of the abdomen revealed probable splenic enlargement. An electrocardiogram was normal except for minor S-T elevation (which was compatible with a mild pericarditis).

Course: The application of tape to the chest gave immediate relief to the pleurisy and helped alleviate the patient's anxiety. A pint of whole blood was given, and amphotericin B, 800 mg. by mouth four times a day, was started. The patient's temperature ranged from 99° to 103° plus during the first three days in the hospital. It then became normal except for two days of spiking fever after the scalene node removal. After one week in the hospital the patient felt much improved and was afebrile. His x-ray showed some clearing. While there was little doubt in our minds of the diagnosis, for epidemiologic and medical-legal reasons it was felt that a cultural demonstration of the organism was highly desirable, and the patient consented to a scalene node biopsy and culture. Large mediastinal nodes were found, and the most distal ones were removed for biopsy and culture. All cultures were positive for *H. capsulatum* (figure 2), and meticulous search of the sections revealed the organism (figure 1). The patient was discharged much improved but still having some twinges of pleuritic pain after two weeks in the hospital. His later complement fixation studies are shown in table 2. He stated that he felt perfectly well three months after his initial attack. Therapy with amphotericin B was continued for three months. Repeat liver function studies on August 22, 1957, were normal. A chest x-ray taken one year after the onset of illness showed that the extensive infiltration seen in both lungs had almost entirely cleared and that the lung fields were approaching a normal appearance (figure 7).

Pulmonary function studies six months after the onset of illness showed ventilation in excess of the normal predicted for a man of this age, height and weight. Blood arterial oxygen saturations were normal at rest and during and after exercise.

Comment: This 20 year old man had an acute attack of histoplasmosis with probable involvement of the lungs, liver, pleura, pericardium and regional lymph nodes. He appears to be making a completely uneventful recovery. Of special interest was the isolation of the organism from the scalene node after failure to isolate it from the sputum, bone marrow and blood. His complement fixation test was positive for blastomycosis but in lower dilution than for histoplasmosis. The role of amphotericin B in his recovery is conjectural, but it is interesting that he was receiving the drug at the time the organism was grown from his lymph node.

Case 9. The patient, a 33 year old carpenter, had been in good health until August 30, 1956, when he noted the onset of malaise and weakness. On August 20 he had assisted in the digging of the footings for the house which was the source of the outbreak. On September 4 he noted the onset of fever, shaking chills, headache, myalgia, sore throat, cough productive of scanty white sputum, and pleuritic chest pain. He was seen by his family physician and given penicillin. On the following day he noted severe generalized pruritus and possibly slight scleral icterus. No rash or jaundice was noted. The pruritus gradually subsided when penicillin was stopped and symptomatic treatment was instituted. Physical examination revealed diffuse minimal râles throughout both lung fields. The liver and spleen were not enlarged, and there were no other abnormal physical findings. The histoplasmin skin test was positive.

On September 7 the fever and chills subsided and the patient had profuse sweating. Shortly thereafter his headache, myalgia and sore throat subsided. Approximately two weeks after onset the other symptoms subsided, with the exception of some malaise and weakness which lasted to a decreasing extent until the end of September.

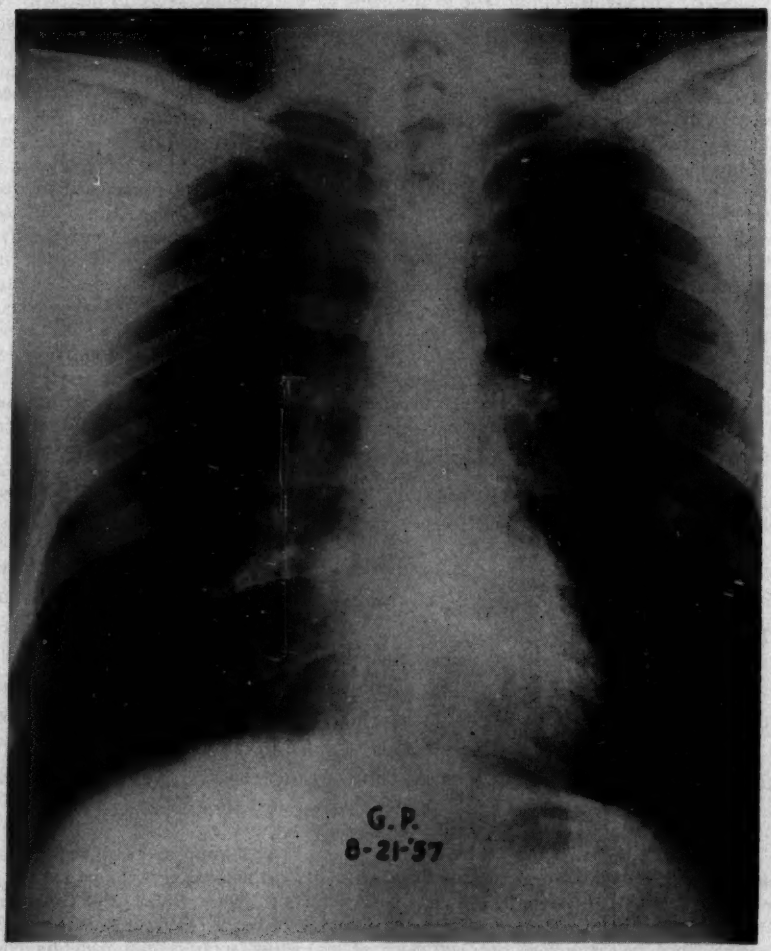


FIG. 7. Chest x-ray of case 8 taken one year after onset. The densities have almost entirely cleared.

On October 4 the patient's first complement fixation test revealed a mycelial titer of 1:16 and a yeast titer of 1:128. By October 18 the complement fixation had fallen to 1:8 and 1:64, and has remained essentially at this value (table 2). The only chest x-ray available was taken on January 10, 1957, and was normal at that time.

Comment: The pruritus could possibly have been due to dissemination of histoplasmosis, but the course of the illness suggests penicillin sensitivity as a more likely cause.

Case 10. The patient, a 46 year old cement contractor, had been in good health until September 4, 1956, when he developed fever, chills, malaise, severe headache, cough, and pain in his chest. On August 20 he had assisted in digging and pouring the footings for the house on the source lot. He was seen by his family physician on September 7 and at this time was afebrile. Scattered expiratory wheezes were noted, but there were no other abnormalities on physical examination. His histoplasmin skin test was positive at this time. On September 10 he was essentially unchanged. His complement fixation at this time was negative in the mycelial phase and 1:8 in the yeast phase. On September 29 it was 1:32 in both the mycelial and yeast phases (table 2). Chest x-ray was read as normal on September 7, 1956, and on January 12, 1957.

The patient was out of work only a few days, but was unable to perform any heavy work or do any lifting for about two weeks. He did not feel normal until mid-November. Some persistent chest pain (pleuritic) was noted over this period, in addition to some weakness and malaise.

Case 11. The patient, a 19 year old mason contracting helper, had been in good health until September 2, 1956, when he noted onset of fever to 101° F., chills, malaise, headache, cough with scant sputum, and slight pleuritic pain. On August 20 he had helped in the digging and the pouring of the footings for the house on the source lot. On September 6 myalgia was noted. On September 7 he saw his family physician. Physical examination at this time revealed no abnormalities except for questionable enlargement of the liver. On September 8 the patient noted steady pain in the anterior chest and was hospitalized. On September 10 the histoplasmin skin test was faintly positive. (On February 27, 1957, the histoplasmin skin test was positive.) The white blood cell count was 10,000; hemoglobin, 14.8 gm.; hematocrit, 47; sedimentation rate, 30 mm./hr. Complement fixation test showed 1:64 titer for both the mycelial and the yeast phases. This persisted until April 29, 1957, when it was 1:8 in the mycelial and 1:16 in the yeast phase (table 2). X-ray showed minimal diffuse miliary lesions. On September 17, 1956, the white blood cell count was 9,900 and the hemoglobin was 13.8. A chest x-ray was unchanged.

The symptoms gradually subsided and the patient was discharged on September 18, 1956. Following discharge, he had intermittent anterior chest pain until mid-October. He was not back to normal health until early November. Chest x-ray on January 10, 1957, showed resolution of the infiltrates.

Case 12. The patient was a 36 year old plumber and the brother of case 2. On August 20, 1956, he had spent one hour at the house in Walworth connecting a sewer pipe. One week later he began to feel malaise and generalized weakness. He had no cough. Twelve days after exposure (September 1) he awoke with a fever and headache that did not respond to aspirin. The next day he developed hard shaking chills that lasted most of the day and were associated with severe sweating. The next day his temperature stayed at 104.8° plus, and the following day he saw his physician, who started penicillin therapy. The fever continued at the same level, and the patient was hospitalized on September 4, with penicillin therapy being continued. At this time he noted severe pruritus of his hands and lower extremities. Laboratory work on September 7 showed a white blood cell count of 12,450 and hemoglobin of 14.6. He remained febrile until September 10, when the fever began to abate. During the next three weeks he continued to have profuse night sweats and a low grade fever, and he lost 30 pounds in weight. In addition, he had a persistent pain in the left upper quadrant, in the region of his

spleen. There was no other pertinent past history. He was transferred to St. Joseph's Hospital because of continued malaise, the weight loss and night sweats. Physical examination on admission revealed an adult white male who appeared to be chronically ill. Temperature was 98.6° F.; pulse, 80; respiration, 16; blood pressure,

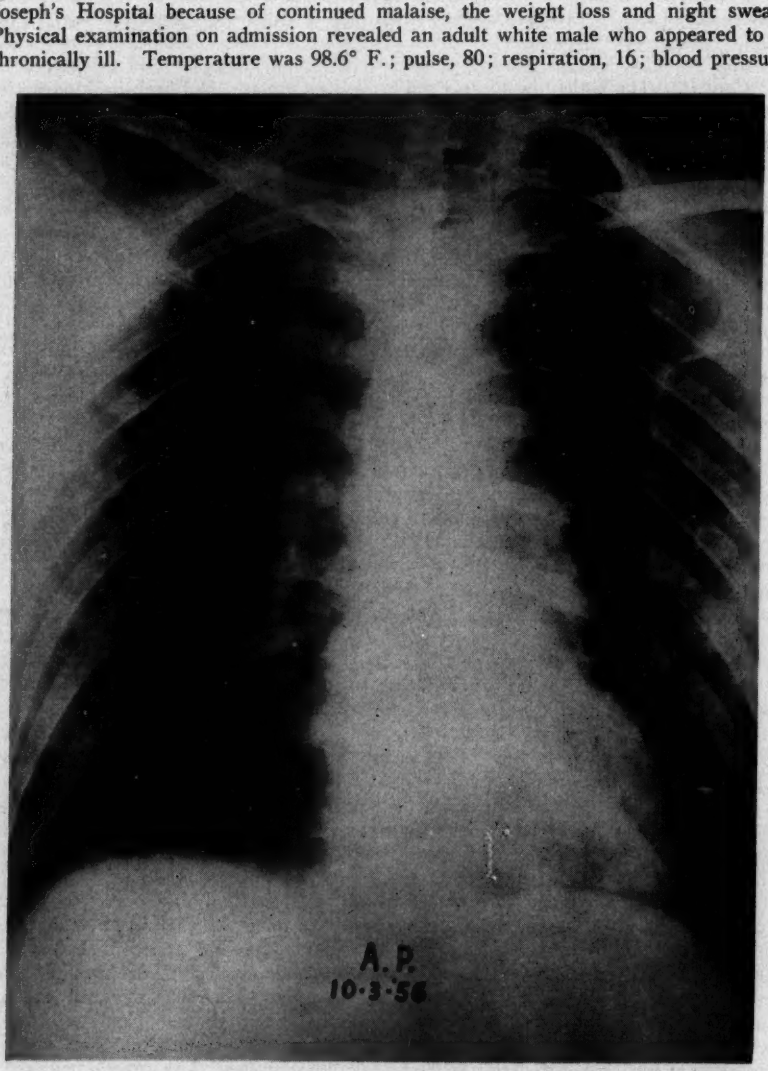


FIG. 8. Chest x-ray of case 12 during the acute illness, showing extensive bilateral infiltrative and nodular lesions.

105/80 mm. of Hg. The lungs appeared to be normal to physical examination. There were hard, 2 cm. lymph nodes in both axillae, which have remained unchanged to the present time. The liver and spleen were not palpable. There was no generalized lymphadenopathy. Laboratory studies were as follows: hemoglobin, 14.4; white blood count, 7,300, with 57% polymorphonuclears, 9% eosinophils and 33%

lymphocytes. Sedimentation rate was 33. Urinalysis was normal. Cultures of the sputum and bone marrow did *not* grow fungi. Complement fixation test for histoplasmosis was negative on September 10, but on September 26 it was 1:64 in the yeast phase and 1:16 in the mycelial phase (table 2). Complement fixation test for blastomycosis was 1:32 on October 10, 1956. Liver function tests revealed a pro-

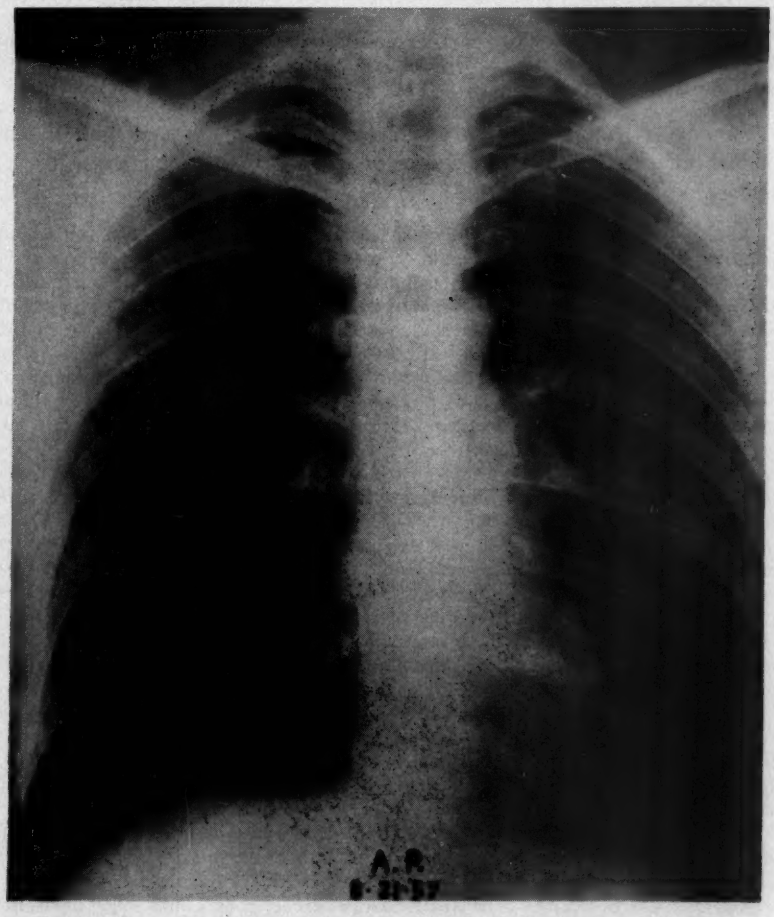


FIG. 9. Chest x-ray of case 12 one year after onset, showing almost complete clearing of lesions.

thrombin time of 90%; nonprotein nitrogen, 32 mg.%; serum protein: 4.9 albumin and 2.6 globulin. Chest x-ray showed a diffuse infiltrative and nodular lesion involving both lung fields (figure 8). Skin test for histoplasmosis was positive on September 7. Bone marrow showed a slight increase in the number of plasma cells.

Course: A scalene node biopsy was done and no organisms were found on section. However, cultures were positive for *H. capsulatum*. The patient was afebrile in

the hospital and appeared to respond to reassurance regarding the nature of his disease. Amphotericin B, 800 mg. three times a day, was started at discharge and continued for three months. The patient did not feel perfectly well until five months after onset, but at the present time he has no complaints. Pulmonary function studies done on April 3, 1957, showed ventilation in excess of the normal predicted for a man of this age, height and weight. Blood arterial oxygen saturations are normal at rest, and during and after exercise.

A chest x-ray taken one year after onset of illness (figure 9) showed almost complete clearing of the lesions and as yet no calcification. Table 2 shows his follow-up complement fixation tests.

Comment: This patient now appears to be clinically well in spite of some residual findings on x-ray. It will be of interest to determine when, if ever, calcification will occur.

Case 13. The patient, a 71 year old carpenter, had been in good health until September 3, 1956, when he noted onset of low grade fever, profuse sweating, malaise, weakness and pleuritic pain. The symptoms were not severe and he continued to work, although he could not work effectively. On August 23 he had inspected the forms at the site of the house on the source lot for about half an hour. The symptoms persisted for about one week and gradually subsided. He did not consult a physician. Shortly after his symptoms subsided he noted a hacking morning cough productive of small amounts of whitish gray sputum, which persisted for about one month. He continued to have varying degrees of malaise and weakness until early December, when he finally felt that he was back to normal. On January 10, 1957, a chest x-ray was normal. The complement fixation test was negative for the mycelial phase and positive at a 1:16 dilution for the yeast phase. Histoplasmin skin test on January 23, 1957, was positive.

Case 14. The patient, a 48 year old carpenter, had been in good health until August 30, 1956, when he noted onset of fever, diaphoresis, malaise, headache and myalgia. On August 23 he had inspected the forms for the foundation of the house on the source lot. The symptoms were prominent for only two to three days, and he was able to return to work. However, he did not feel completely well, and on September 13 he noted onset of cough and pleuritic pain which persisted for about one week. He returned to normal health at about the end of September.

On September 10 the histoplasmin skin test was positive. The complement fixation test was 1:8 in the mycelial and 1:16 in the yeast phase. On January 11, 1957, the complement fixation test was 1:16 in the mycelial and 1:32 in the yeast phase (table 2). An x-ray on September 17 showed prominence of the right hilum and some scattered densities bilaterally.

Case 15. The patient, a 58 year old carpenter, had been in good health until August 30, 1956, when he noted the onset of fever, chills, malaise and myalgia. He also had inspected the forms for the basement of the house on the source lot on August 23. On September 2 he also noted headache, cough, and some intermittent chest pain (pleuritic?). Examination by his family physician on September 7 revealed scattered râles bilaterally but no other abnormal physical findings. The histoplasmin skin test was "? positive" at this time. (On January 23, 1957, it was positive.) A chest x-ray at this time revealed "suspicious nodularities" bilaterally. After September 8 the illness began to subside, and by the end of the second week most of the symptoms were gone. The patient continued to have malaise and weakness, however, and was not in normal health until the end of October. Repeat x-ray on September 22 confirmed the presence of nodular densities throughout both lung fields.

On September 12 the complement fixation test was positive in a titer of 1:32 in the mycelial and 1:64 in the yeast phase. It remained at this level until April 29, 1957, when it was negative in the mycelial and 1:8 in the yeast phase (table 2).

Case 16. The patient was a 22 year old student who worked summers as an apprentice carpenter. He also inspected the forms for the basement of the house on August 23. He had been in good health until September 7, 1956, when he noted the onset of malaise and mild myalgia. Two days later he noted fever to 102° F., chills and headache. He also noted intermittent sweating, cough, and a tight, nonpleuritic chest pain. On September 14 physical examination revealed scattered râles bilaterally, but no other abnormalities were found. He was treated with oxytetracycline and erythromycin. A histoplasmin skin test was positive at this time. Chest x-ray was normal. On September 22 the histoplasmin complement fixation test was positive at 1:8 titer for the mycelial and 1:16 titer for the yeast phase. On April 23, 1957, the complement fixation test was negative in the mycelial and 1:8 in the yeast phase. The patient's fever had subsided approximately two weeks after onset. However, he still complained of weakness and had lost about 15 pounds. He entered the first year of medical school in October and complained of lacking pep throughout the first quarter. By the end of December he was beginning to feel normal again.

Comment: The previous four patients (cases 13, 14, 15 and 16) were working during the month of August on the roof of the house next door to the site of the outbreak. There was an opportunity for exposure at any time during this month. However, when questioned separately, the only time any of the four men could remember being on the source lot was on August 23. It is therefore assumed that this was the time of exposure, since the incubation period of all four would then fall within the commonly accepted limits.

Case 17. The patient, a 27 year old plumber, had been in good health until November 23, 1956, when he noted the onset of fever to 102.5° F., weakness and malaise. On November 9 he had laid sewer pipe in a ditch dug in the basement of the house on the source lot. On November 27 he began noting shaking chills, diaphoresis, headache and myalgia. Physical examination on December 3 revealed a few "dry" râles bilaterally, but no other abnormalities were found. Chest x-ray revealed diffuse nodules bilaterally. Penicillin and chloramphenicol therapy was begun. The next day the patient noted dyspnea on rest and was admitted to the hospital. In the hospital penicillin and novobiocin were substituted for the above. Bone marrow biopsy performed on December 5 was negative for *H. capsulatum* by microscopic examination and culture. The patient remained essentially unchanged in the hospital except for occasional slight cough. On December 10 the histoplasmin skin test was positive, and the complement fixation test was positive at a titer of 1:16 in the mycelial and 1:64 in the yeast phase. On this day he left the hospital. By December 14 the fever and most of the symptoms had subsided with the exception of exertional dyspnea, cough, and nonpleuritic chest pain. In addition, the patient noted small amounts of gray, viscous sputum. By the end of December his chest x-ray showed clearing of the peripheral lesions, with some enlargement of the right hilum, and his dyspnea was decreasing. He had an episode of pleuritic pain for four days in early January, 1957. He was able to return to work by mid-January, but continued to note exertional dyspnea for about another month. He has gradually recovered and is in normal health at present.

Case 18. The patient, a 27 year old real estate salesman, had been in good health until November 25, 1956, when he noted the onset of malaise, fever, chills, sweating,

headache and myalgia. He had visited the basement of the house on the source lot on November 9, when the sewer line was laid. By November 28 he noted onset of cough and pleuritic pain. He had a history of chronic bronchiectasis, and assumed that his present illness was related to this. On November 30 physical examination revealed some dullness and increased breath sounds in both bases, and scattered "dry" râles throughout both lung fields. No other abnormalities were found on physical examination. Therapy with penicillin and tetracycline was begun. On December 3 the white blood cell count was 11,000; red blood cell count, 4.65 million; sedimentation rate, 30 mm./hr. The histoplasmin skin test was positive on December 8. The patient lost 12 pounds during his illness. He was able to return to part-time desk work by December 10, and by the end of December was feeling normal again. He still noted occasional brief episodes of pleuritic chest pain in January, 1957. On February 8, 1957, complement fixation test showed 1:4 titer in the mycelial and 1:128 titer in the yeast phase.

Case 19. The patient, a 55 year old health officer, had been well until September 23, 1956, when she noted the onset of low grade fever, malaise, weakness and headache. During the following week she noted pleuritic pain and cough. On September 8 she had taken soil samples from the site of the epidemic. At the time the illness was not recognized and she gradually recovered. By October 15 she had returned to normal health. In March, 1957, a routine chest x-ray at a mobile unit was read as suspicious for pulmonary carcinoma. In April a diagnosis of histoplasmosis was made on the basis of history, appearance of x-ray, positive skin test, and a complement fixation titer of 1:4 in the mycelial and 1:16 in the yeast phase. Repeat complement fixation test on June 11, 1957, was negative in the mycelial and 1:4 in the yeast phase. The patient is now feeling well.

Discussion

The epidemic that has been reported offered a unique opportunity to study a sizable outbreak of histoplasmosis among groups of persons with varying times of exposure. The exact date and extent of exposure of each case were determined, and therefore our findings of the range of seven to 16 days for the incubation period and of a direct relationship between extent of exposure and severity of illness have particular validity.

The lack of a history of exposure to an old enclosure or to chicken or bird droppings is worthy of comment, and should emphasize the fact that these usual sources of exposure in histoplasmosis are not necessary for cases or outbreaks of the disease. The danger of the area that was infected to the people in the community was emphasized by the fact that the public health physician who gathered the specimens of soil for culture herself acquired the disease, as did the plumber who volunteered to finish the basement after the epidemic was known. In this case fresh top soil was bulldozed over the front lawn area, but if in other instances larger areas of infection should be found the problem could not be handled in this manner. At present there appear to be no adequate means to treat the soil to render it safe.

The favorable prognosis of acute epidemic histoplasmosis is emphasized by our series, which showed that by one year after the disease every individual was back at work without complaint. X-ray findings were

markedly improved but still present in many patients. This is in contrast to the Camp Gruber epidemic, in which a much greater percentage of permanent disability was noted.[29] This may have been related to the particularly heavy exposure in that epidemic. However, a long-term follow-up with pulmonary function studies will be necessary to rule out the possibility that future pulmonary difficulties may show up in some of our patients. Other reports in the literature have found, as we did, that permanent disability apparently is rare in histoplasmosis.[6, 30] The evaluation of amphotericin B in the three patients who received it was not possible. They have done well, but so have the untreated patients.

Several points regarding diagnosis are worthy of comment. The first is the importance of persistence in obtaining cultural evidence of the disease. In our cases, resort to culture of scalene nodes was necessary, since cultures of the sputum and bone marrow were negative and the initial histologic examination of the scalene nodes did not reveal the organism. The value of obtaining positive cultures from the soil samples for epidemiologic as well as possible medical-legal reasons should be obvious. Skin tests and complement fixation tests done in a serial manner also were important factors in the clinical and epidemiologic evaluation of this epidemic. In two cases the complement fixation test was positive for blastomycosis as well as histoplasmosis. In both of these cases the scalene nodes grew *H. capsulatum*. This should serve as a reminder that there is some cross antigenicity between these diseases, both of which have occurred in this region. It is our experience [31] that the clinical picture may be similar, and that the diagnosis of both of these diseases in sporadic cases should be substantiated by cultural findings when possible. When this is not possible, diagnosis should be based on evaluation of clinical, epidemiologic and serial serologic studies against antigens of both blastomycosis and histoplasmosis.

The value of epidemiology as an aid in diagnosing histoplasmosis is well illustrated by this outbreak. Once the diagnosis was made in case 1 and made known to the local physicians, the presence of other cases became apparent to them. These cases had been diagnosed as pneumonia or pneumonitis of unknown etiology until the diagnosis of histoplasmosis was suggested and association with the proposed site of infection was made. Case 19, the public health physician, who was discovered many months after the outbreak, might have undergone needless surgery for carcinoma of the lung on the basis of chest x-ray if it had not been known that she was a contact to the site.

The occurrence of small localized areas of soil with a heavy inoculum of *H. capsulatum* outside known endemic areas may be more common than has heretofore been realized. Therefore, it behooves all physicians to have a high index of suspicion for histoplasmosis in cases with unexplained pneumonitis. Early epidemiologic follow-up, coupled with the simple tests necessary to aid in establishing a diagnosis of histoplasmosis, may lead to

the discovery of other outbreaks such as this and assist in clarifying the pattern of infection in nonendemic areas.

Summary and Conclusion

An epidemic of histoplasmosis that involved 19 persons in Walworth, Wisconsin, has been reported. The organism was isolated from the soil surrounding the house which the patients were building and from the scalene nodes of two patients. The incubation periods, relationship between the extent of exposure and illness, the clinical pictures, roentgenographic findings and laboratory results were presented. A skin test survey of the area suggests a rather discrete area as the source of infection, but the circumstances by which organisms gained entry into this area could not be determined. The importance of complete cultural as well as serologic studies in epidemic situations, the relative benignity of histoplasmosis and the potential dangers of such discrete areas infected with *H. capsulatum* were emphasized.

Acknowledgments

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Summario in Interlingua

Es reportate un epidemia de histoplasmosis a Walworth in Wisconsin, afficiente 19 personas in le curso de tres menses. Dece-octo esseva associate con le construction de un nove casa in le communitate. Le dece-none esseva un medico del servicio de sanitate public qui obteneva specimens de solo ab le sito del construction. *Histoplasma capsulatum* esseva isolate ab le scalen nodos lymphatic in duo casos. Specimens de solo al sito de construction esseva culturate a quatro differente occasiones, e quatro vices le presentia del organismo esseva demonstrate.

Le periodo de incubation variava inter septe e 16 dies. Le declaration del morbo esseva marcate in le majoritate del casos per febre, malaise, debilitate, e mal de capite. Cinque patientes habeva un periodo prodromal de malaise e debilitate ante le declaration de febre. Mal de capite, debilitate, myalgia, e—in certe casos—dolores pleuritic esseva le symptomas le plus prominente. Tusse, dyspnea, e non-pleuritic dolores thoracic esseva etiam frequente sed non sever. Le constatationes physic esseva minimal, excepte in cinque casos: tres con hepatomegalia, un con leve grados de conjunctivitis, e un con ruito de friction pleuro-pericardial.

Roentgenogrammas thoracic esseva obtenite ab 13 patientes durante le phase acute de lor morbo. Dece-tres roentgenogrammas monstrava lesiones parenchymal, duo monstrava solmente lymphadenopathia hilar, e un esseva interpretate como normal. Calcification non appareva durante le prime anno de observation post-epidemic. Esseva effectuate tests de fixation de complemento con le phase mycelial e etiam con le phase saccharomycetic. Illos produceva resultatos positive durante le periodo ab le secunde usque al quarte septimana del morbo. Le titros maximal esseva attingite in omne casos al fin del quarte o quinte septimana. Post le quinte mense

del morbo, le titros comenciava redescender gradualmente, sed illos esseva ancora positive al fin del anno, ben que con basse titros.

Un scrutinio communal per tests cutanee a histoplasmina produceva un plus alte procentage de positivitate in le area del village ubi le foco del epidemia esseva trovate que inter le altere habitantes. Il es probabile que le 19 casos del presente reporto non esseva le soles inficite per le mesme foco.

Iste epidemia es de interesse special proque le foco del organismo se trovava in un area aperte. Le majoritate del epidemias reportate in le litteratura prende lor origine in areas claudite. Le isolation del organismo ab scalen nodos lymphatic de duo patientes con negative biopsias de medulla ossee suggere que iste methodo es a recommendar pro le isolation del organismo causal in casos in que le demonstration del etiologia es specialmente desirabile. In le majoritate del casos in le presente epidemia, le diagnose se suggereva a causa de un historia de activitate commun del patiente in question con ille del prime caso identificate. Es opinate que considerationes epidemiologic pote esser de ver valor in le diagnose de histoplasmosis.

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CLONORCHIASIS SINENSIS: CLINICAL MANIFESTATIONS AND DIAGNOSIS*

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CHINESE medicine has had many lessons for Western observers,[1] some of the most interesting having been in the various parasitic diseases. During the last several years a number of papers have appeared, particularly in the foreign literature, regarding the diagnosis and therapy of human clonorchiasis. The purpose here will be to clarify the clinical picture as seen in two large teaching hospitals in this country, and to discuss the newer diagnostic technics.

Endemic areas of heavy human infestation are Japan, Tonkin Indo-China and the Kwongtong Province of South China.[2, 3] The incidence of human infestation has been estimated to be as high as 80% in Canton, China, with a total world incidence of 19,000,000.[3] Other endemic areas are Formosa and South Korea.

The life cycle was first delineated in 1927.[4] Ova-laden feces shed in fresh water pass through the stage of ciliated miracidia. After molluscan ingestion by an appropriate snail, the trematode successively passes through the stages of sporocyst and second-generation redia. Free-swimming cercariae are then liberated and, after coming into contact with a suitable fresh-water fish host, penetrate the scales and encyst in the flesh as metacercariae.[5] Man becomes involved when infested raw, smoked or steamed fish is eaten. After digestion by gastric juice, the cysts liberate actively motile larvae which travel from the duodenum up the common bile duct to mature eventually in the smaller biliary radicles.

The endemic areas previously noted are economically poor. This has shaped the eating habits of the native population. One of the dietary staples is fish, necessarily eaten raw or lightly steamed, since firewood is scarce and prohibitively expensive. Being a frugal race, the Chinese are in the habit of raising fresh water fish in ponds dug under mulberry trees. The trees are then fertilized by human night soil, which contaminates the water and completes the cycle. Cats, rats, dogs and cattle also serve as a reservoir for the parasite.

As in any other disease entity, a wide spectrum of clinical manifestations exists.

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Case Reports

Case 1. A 41 year old male Cantonese with proved adenocarcinoma of the lung was noted to have 6% to 12% peripheral eosinophilia as an incidental finding. Examination of the stool revealed *Clonorchis sinensis* ova. He had come from Canton, China, 20 years previously, had not eaten raw fish in the interim, and no complaints referable to parasitic infestation were noted. Physical examination and laboratory data revealed only the presence of adenocarcinoma of the lung. There was no hepatomegaly. Liver function survey was normal.

Case 2. A 59 year old male had spent several years in Shanghai, China, eating raw fish while there. His chief complaint upon admission in 1956 was aching right upper quadrant pain of 11 years' duration. A diagnosis of clonorchiasis had been made several years prior to admission. Treatment with atabrine, gentian violet and diodoquin was ineffectual. Physical examination revealed a large, nontoxic goiter and two-fingerbreadth hepatomegaly with a sharp, smooth, firm, slightly tender edge. Delayed punch tenderness was present over the hepatic area. A 6% peripheral eosinophilia was noted, as was a 3 plus cephalin flocculation. Several stool examinations revealed numerous *C. sinensis* ova. Oral cholecystography was normal. Poor biliary flow was noted during duodenal aspiration. The patient was treated with Milibis, chloroquine and atabrine. The stools remained ova-positive, and the right upper quadrant pain persisted. Liver biopsy revealed normal liver tissue.

Case 3. This patient had lived in the Kwongtong province as a youth. He entered with a two-year history of gripping right upper quadrant pain, fatigue, anorexia and weight loss. Right upper quadrant guarding with delayed hepatic area punch tenderness was noted; no hepatomegaly was present. No eosinophilia was present. Oral cholecystography failed to visualize the gall-bladder. Survey of hepatic function was normal. Stools were persistently positive for *C. sinensis* ova. Treatment with intravenous gentian violet was unsuccessful in alleviating the pain or clearing the stool.

Case 4. A 45 year old Cantonese male entered with a four-month history of right upper quadrant pain of a dull, aching nature, fatigue and anorexia. He was an emaciated Chinese with a three-fingerbreadth hard, nodular, nontender liver. Laboratory data showed a hemoglobin of 7 gm.% and a white blood cell count of 24,200, with no eosinophilia. Hepatic function survey was normal. Stools were positive for Clonorchis ova. Liver biopsy was interpreted as showing cirrhosis secondary to *C. sinensis* parasitism with superimposed hepatocellular carcinoma.

Case 5. A 51 year old Cantonese laundryman with a left cheek mass was noted to have persistent eosinophilia ranging between 6% and 30%, and a several-year history of dull aching right upper quadrant pain. There was no hepatomegaly. Liver survey was normal except for transient 3 plus cephalin flocculation test. Repeated stool examinations failed to reveal Clonorchis ova, although on duodenal drainage the trematode eggs were found.

Case 6. A 46 year old Cantonese laundryman had last eaten raw fish in 1930, 27 years before hospitalization. The intervening period had been asymptomatic. In October, 1956, there was a sudden onset of epigastric pain that radiated through to the back and then localized in the right upper quadrant. The pain was associated with nausea, vomiting and a distaste for cigarettes. He was an obese, febrile, acutely ill, icteric Chinese male with decreased bowel sounds, epigastric tenderness and clay-colored stool. Hemoglobin, 15 gm.%; white blood cells, 16,300; 0% eosinophilia. Bile and urobilinogen were noted in the urine. Stool guaiac test was negative, and no ova, cysts or parasites were noted on stool examination. Amylase, 128;

lipase, 1.9; total protein, 7.5. A/G, 4.6/2.9. Cholesterol/esters, 400/300; alkaline phosphatase, 18.0; thymol, 4.8; cephalin flocculation, negative; prothrombin, 81%; heterophil, negative; fasting blood sugar, 94; blood urea nitrogen, carbon dioxide, sodium, potassium, chlorine, calcium and phosphorus were normal, as were an electrocardiogram, chest and abdominal films, and a gastrointestinal series. One week after admission increasing jaundice, anemia and guaiac-positive stools were noted. The bilirubin was 16; thymol, 10.4; alkaline phosphatase, 25; hemoglobin, 9. Duodenal aspiration revealed no crystals, ova, cysts or parasites. It was felt that the patient had ampullary carcinoma, and he was transferred to the Surgical Service. While there he suddenly developed nausea, vomiting, right upper quadrant pain that radiated through to the back, a 23% eosinophilia and an amylase of 648. After the episode of acute pancreatitis had subsided, exploratory laparotomy was performed. The liver appeared to be normal. The gall-bladder and the common and cystic ducts were acholic but otherwise normal. The right hepatic duct was completely obstructed to probing, the left partially so. No free biliary flow was noted until two hours after the probing. A T-tube was inserted. A liver biopsy was taken and read as "evidence of bile canalicular obstruction with marked eosinophilia." On the seventh postoperative day the biliary drainage was examined microscopically and found to contain numerous *C. sinensis* ova. Following transfer back to the Medical Service, barium enema and proctoscopy were found to be normal. After treatment with 39 gm. of chloroquine, 10.5 gm. of Milibis and 2.5 gm. of gentian violet, all laboratory data became normal and ova were no longer found in the biliary drainage. After normal cholangiography the T-tube was removed and the patient discharged with instructions to return in six months for reëvaluation.

Case 7. A 53 year old male Chinese kitchen worker with documented lymphosarcoma presented with a five-year history of intermittent sharp right upper quadrant pain, anorexia and increasing fatigability. His last exposure had been in Canton in 1933. Physical examination revealed generalized lymphadenopathy and a two fingerbreadth, firm, nontender liver. Stool examination was negative for ova and parasites. Duodenal aspirate showed larvae of *Strongyloides stercoralis* and ova of *C. sinensis*. A 10% peripheral eosinophilia was present. Liver biopsy showed no evidence of lymphosarcoma. The liver function tests were all within normal limits. The patient was treated with chloroquine diphosphate.

Case 8. A 41 year old Hungarian-born white female immigrated to Shanghai, China, in 1939. While there she was discovered to harbor *C. sinensis*. Atabrine therapy was of minimal value. Admission to the Gynecology Service in 1949 was for an incomplete abortion. Dilatation and curettage were performed. Physical examination revealed a smooth, firm liver edge 2 cm. below the right costal margin. Stools were positive for Clonorchis ova. A 3% peripheral eosinophilia was noted; liver function tests were normal. Skin test with fasciola extract was positive. Treatment with Hetrazan (diethylcarbamazine) temporarily cleared the stool of Clonorchis ova. A cholecystogram was normal. The patient was re-admitted in 1952 complaining of weakness, dyspepsia and right upper and lower quadrant abdominal pain. A 10-day course of Fuadin was ineffectual in clearing the stool of trematode ova.

Discussion

The foregoing cases emphasize the wide spectrum of clinical manifestations in human clonorchiasis as seen in this country.

Infestations may be classified as (1) asymptomatic cases discovered on routine stool examinations, with or without eosinophilia, and (2) sympto-

matic cases presenting with as little as right upper quadrant pain, or as dramatically as complete obstructive jaundice and acute pancreatitis.

Case 1 was completely asymptomatic. There were no physical findings referable to parasitism. The peripheral eosinophilia prompted a stool examination for ova, cysts and parasites, and *C. sinensis* eggs were fortuitously discovered. Eosinophilia is not, however, an invariable occurrence, and heavy infestations have been noted with a normal peripheral blood picture, as exemplified by case 3.

The most common symptomatology, noted in this series of eight cases, was a long history of right upper quadrant pain of a dull, gripping nature, anorexia, fatigue and some weight loss. This is by no means the most common clinical picture in an endemic area, where as high as 80% of the population is infested, and the majority of these cases are asymptomatic.[8] Cases 2, 3, 4, 5, 7 and 8 demonstrate the most common clinical picture in our series. These patients had symptoms of long duration, the most prominent being dull, mild to moderately severe right upper quadrant pain. Only cases 2, 4, 7 and 8 were noted to have hepatomegaly. The presence of abdominal pain and anorexia in nonicteric individuals with essentially normal liver function tests has been reported by previous observers.[2, 6, 7]

TABLE 1

Manifestation	Number of Cases
Endemic area residence	8
Right upper quadrant pain	7
Normal liver function tests	5
Anorexia and weight loss	5
Eosinophilia	5
Positive stool	5
Hepatomegaly	4
Positive duodenal drainage, negative stool	3

Cases 1, 3, 4, 7 and 8 had normal liver function tests. Cases 2 and 5 had only abnormal cephalin flocculation tests. This has not been the experience of previous observers, who note that hepatocellular dysfunction can be demonstrated by bromsulfalein retention, positive flocculation tests and the presence of elevated and abnormal globulins. In a series of 132 cases from the German Cross Korean Hospital, 59% of the patients showed evidence of liver damage by elevated thymol turbidity and bromsulfalein retention. However, many of these patients had evidence of malnutrition, which undoubtedly was a factor in their liver disease. Portal and/or biliary cirrhosis has been reported in patients with long-standing infestation.[5] Intrahepatic calculi have also been reported in hepatic clonorchiasis.[5]

Chronic cholecystitis and cholelithiasis are not uncommonly noted, and are believed to be related to biliary stasis and chronic biliary tract infection. It has been noted that bacterial superinfection of the biliary tree with *Escherichia coli* causes the complications of cholangitis and calculi.

Adenomatous tissue formation of the biliary duct is a complication of

heavy, short-duration infestation, and has been reported to give rise to primary hepatocellular carcinoma.[5, 8] Case 4 illustrates that hepatic clonorchiasis may cause cirrhosis and be associated with primary hepatic carcinoma.

At the opposite end of the clinical spectrum exist the signs and symptoms noted with complete biliary obstruction and acute pancreatitis. Case 6 presented with a sudden onset of complete extrahepatic biliary obstruction with hypochromic microcytic anemia and guaiac-positive stools. In the presence of a normal radiologic study of the entire gastrointestinal tract and normal proctoscopic examination, it was felt that the blood loss anemia was secondary to parasitic infestation of the biliary tree. Icterus is an uncommon finding in clonorchiasis, and occurs only where the parasite obstructs the biliary flow.[6] The larvae mature in the smaller biliary radicles, but viable adult worms have been found in the gall-bladder and the pancreatic ductile system, always in association with numerous worms in the common bile duct. Case 6 demonstrated that, with complete biliary obstruction, the stool and the duodenal aspirate are usually negative for the operculated ova. As soon as surgical removal of the obstructing parasite was performed, the ova appeared in great numbers from the T-tube drainage. This case also demonstrates the long asymptomatic period between initial infestation and clinical symptoms. His last ingestion of raw fish had been 27 years prior to the present admission. The ability of the trematode to exist in an asymptomatic fashion for a period of 35 years has been documented.[6]

It should be noted that direct man-to-man transmission is not possible. Two intermediate hosts are required to complete the life cycle, and the parasite can be acquired by man only by eating infested, improperly cooked or raw fish. Since the importation of raw fish from the Orient is prohibited by Federal law, all observed cases of clonorchiasis in the United States have been in people who have lived in or passed through an endemic area. Potentially suitable snail and fish hosts do exist in this country, and the parasite could theoretically become established in the United States.[15]

In this series, and in all cases heretofore observed in this country, the patients have fallen into one of two ethnic groups: Orientals, or European Jews who immigrated to Shanghai. An epidemic of clonorchiasis was reported in 1946 from Shanghai in a colony of displaced persons. These were Jews who ate raw fresh-water fish falsely sold as "herrings." An acute clinical picture was described consisting of fever, malaise and tender hepatomegaly. Several patients developed jaundice and splenomegaly. A 10% to 40% peripheral eosinophilia was noted; Clonorchis ova were found in the fourth week of the illness in either stools or duodenal aspirate. This epidemic has been the subject of previous reports.[2, 15] Both Caucasians reported here were involved in the Shanghai epidemic. Six of these eight cases were of Chinese extraction, and had lived for some part of their early lives in the Kwongtong Province of China.

The diagnosis of clonorchiasis should be entertained in anyone presenting any of the above noted clinical pictures, associated with an explained eosinophilia, a history of raw-fish ingestion, and residence in an endemic area.

The actual diagnosis may be substantiated in one of five ways. The sine qua non is the demonstration of the operculated ova (figures 1 and 2). Stool examination, using formaldehyde sedimentation technics, is the oldest

FIG. 1. Ova of *Clonorchis sinensis*. Actual size of these small operculated eggs is 30 μ by 15 μ (1300 ×).

and easiest of all methods but suffers in two respects: the ova must have access to the duodenum, and even heavy infestations are likely to be missed. Three of the eight cases herein reported manifested negative stool examinations for the operculated ova, and only after duodenal drainage was performed was the diagnosis made. Duodenal drainage of biliary secretions offers the advantage of obtaining unmacerated ova in "pure culture" concentrate. Intradermal testing with ground trematode antigen,[7] while convenient and suitable to mass screening, gives occasional false-negative results. A positive reaction always means infestation by trematode, but does

not distinguish between *Paragonimus westermani, Fasciolopsis buski* and *Clonorchis sinensis* infestation.[7] Complement fixation tests have also been described in the Chinese literature.[7] This is a time-consuming research tool which does not give accurate results. It should be noted that intradermal and complement fixation antigens are not commercially available in this country. Finally, intravenous cholangiography may demonstrate adult trematodes in the larger biliary passages and common bile duct.

FIG. 2. Ova of *Clonorchis sinensis*. Contents of duodenal drainage from case 6 (240 ×).

A review of the literature reveals that therapeutic agents used in the past have been gentian violet, sodium antimony tartrate, potassium antimony tartrate, carbarsone, extract of aspidium, pelletierine, thymol, picric acid, emetine hydrochloride, gold preparations, atabrine, Milibis and chloroquine diphosphate.[14, 16, 17] At present chloroquine diphosphate in a dosage of 30 to 35 gm. over a seven- to eight-week period (250 mg. twice a day) is the therapy of choice.[6, 7] Higher dosage schedules have been employed but often produce anorexia, nausea, vertigo, blurred vision, diplopia, malaise, and pruritus.

A recent series of 90 cases has been reported from China in which there

was an 84.4% cure rate on a short-term follow-up with the use of chloroquine in a dosage of 400 or 600 mg. a day for 35 days to a total dose of 20 to 22 gm. These observers note that a negative post-treatment duodenal aspirate is a more sensitive indicator of cure than is a negative stool examination.[14]

It has been postulated that the therapeutic efficacy of chloroquine diphosphate in trematode infections is due to transient sterilization of the adult flukes. In a recent study from Thailand dealing with *Opisthorchis viverrini* infestation, chloroquine has been found to be of value. The life cycle and clinical manifestations of this parasite greatly resemble those of *C. sinensis*.[18]

No case can be classified as cured until at least a six-month follow-up has been obtained.[10] If relapse is proved, retreatment should be instituted.

Summary

Clonorchiasis is a not uncommon disease as seen in two large teaching hospitals in the eastern United States. Four of the eight cases herein reported were observed by the authors over a one-year period.

The background of endemic area residence, unexplained eosinophilia associated with symptoms of right upper quadrant abdominal pain, anorexia and weight loss should raise the index of clinical suspicion and prompt diagnostic studies.

Eight case reports are presented of patients infested with this parasite which demonstrate the clinical spectrum of disease manifestations. A case associated with primary hepatic carcinoma and another presenting with obstructive jaundice and acute pancreatitis have been reported.

Modes of diagnosis and therapy have been presented and the literature has been briefly reviewed.

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Summario in Interlingua

Clonorchiasis chinese es un morbo non incommun, a judicar per observationes in duo grande hospitales universitari in le Statos Unite oriental. Quatro del octo casos reportate in iste articulo esseva observate per le autores in le curso de un periodo de un anno.

Le serie total demonstra le extension del spectro clinic de iste morbo. Illo include un caso associate con carcinoma hepatic primari e un altere a presentation con jalnessa obstructive e pancreatitis acute.

Le factores que debe inspirar le suspicion de un diagnose de clonorchiasis es un historia de residentia in un area endemic, inexplicate eosinophilia associate con dolores abdominal in le quadrante dextero-superior, anorexia, e perdita de peso. In lor presentia le prompte initiation de studios diagnostic es indicate.

Le methodos diagnostic que es currentemente in uso include:

1. Examine del feces pro le presentia de ovos.
2. Aspiration duodenal pro determinar le presentia de ovos.
3. Tests cutanee (intradermal).
4. Tests a fixation de complemento.
5. Cholangiographia intravenose pro visualisar le trematodo adulte.

Inter istos, solmente methodos (1) e (2) produce resultatos decisive.

Al tempore presente, le droga de election in le therapia initial es diphosphato de chloraquina.

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CASE REPORTS

PERICARDITIS WITH EFFUSION: NEW OBSERVATIONS, WITH A NOTE ON EWART'S SIGN *†

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Recent observations following angiocardiography in patients with pericardial effusions reaffirm that small effusions accumulate in the infracardiac diaphragmatic portion of the pericardial sac. With larger effusions, the fluid next accumulates anteriorly in the retrosternal area because of fixation of the pericardium to the great vessels above, and by the inferior vena cava as it pierces

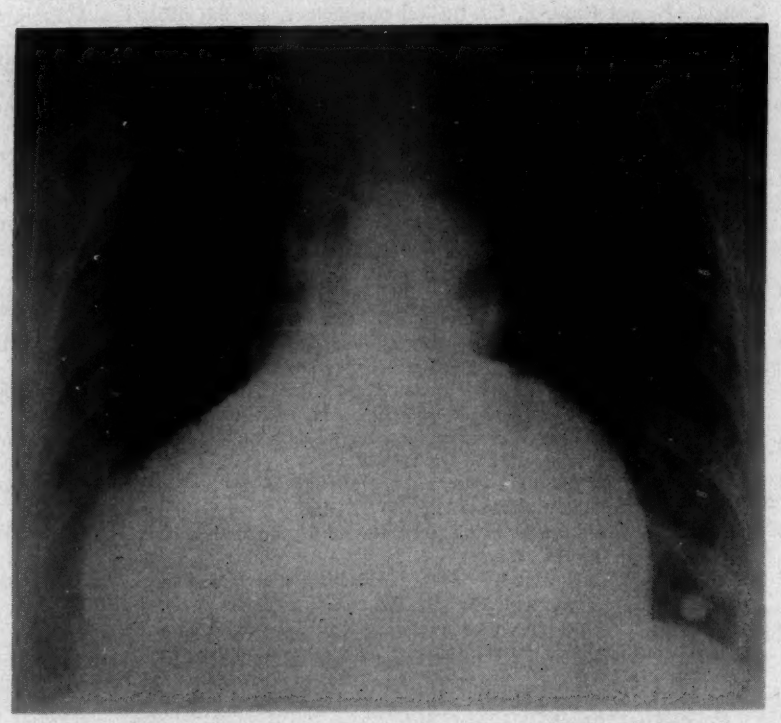

Fig. 1A. Massive chronic pericardial effusion in a 59 year old woman. Frontal erect teleroentgenogram shows a markedly distended pericardium, especially on the right.

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the diaphragm below. With massive effusions, the lateral pericardial pouches become distended. In light of this information, a note concerning Ewart's sign and thoracic paracentesis through the posterior approach seems warranted.

Ewart in 1896,[1] and Pins [2] before him, called attention to the presence of an area of variable size with dullness in the region of the inferior angle of the left scapula associated with a corresponding area of bronchial breathing, increased fremitus and egophony in pericardial effusions. Ewart attributed the signs to partial collapse of pulmonary tissue and pressure on a bronchus.

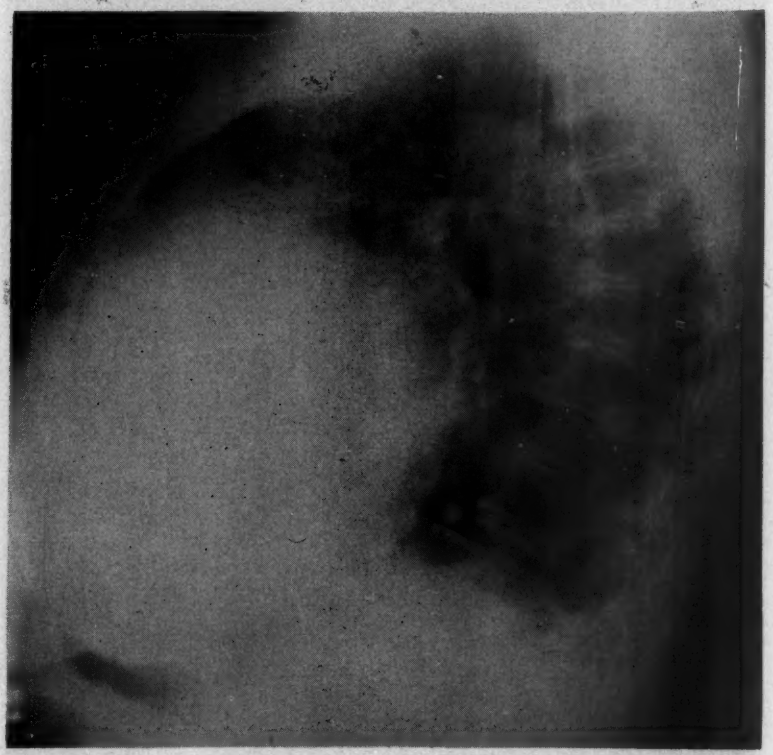

FIG. 1B. Left lateral erect teleroentgenogram shows the retrosternal location of the pericardial fluid. Calcifications, left base, are probably due to old tuberculosis.

Figures 1A and B are the frontal and lateral conventional roentgenograms taken in the erect position of a 69 year old woman with a massive pericardial effusion of long standing who had a positive Ewart's sign. Figures 2A, B, C, and D are the frontal and lateral angiocardiograms made in the erect position. The frontal view shows the classic appearance of pericardial fluid surrounding the heart (figures 2A and B).[3, 4] In the lateral views (figures 2C and D) the pericardial fluid is entirely anterior and does not surround the posterior part of the heart. The position of the cardiac chambers and great vessels within the

distended pericardium in this case was also verified by operation, the pericardial fluid being free and nonloculated. Figure 3 is the postoperative film showing the heart to be normal in size and configuration, indicating that the enlarged cardiac silhouette was due to the pericardial effusion.

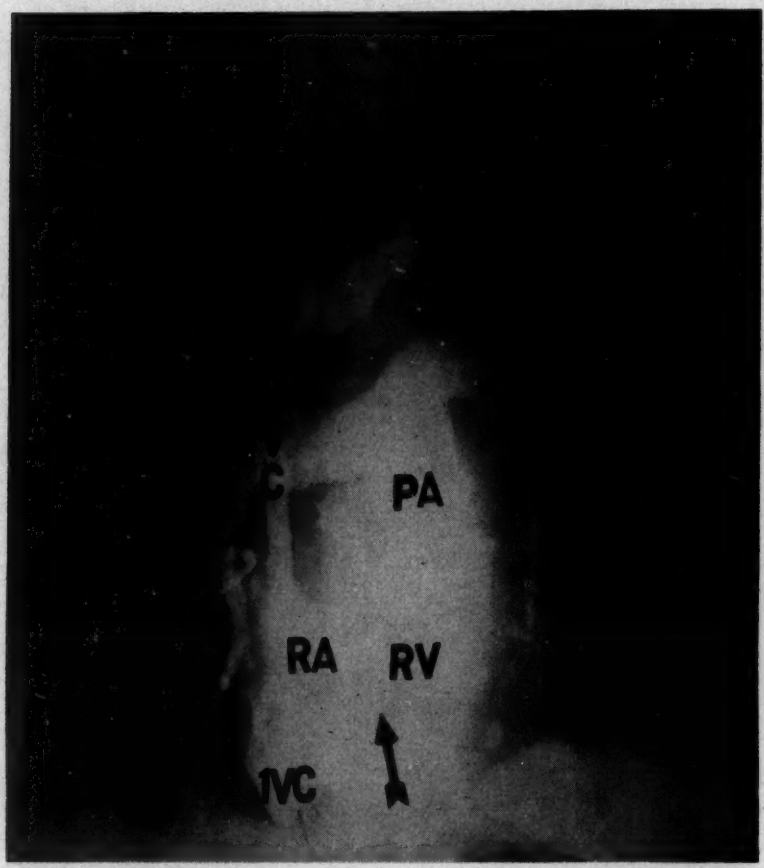

FIG. 2A. Erect teleroentgenangiocardiogram, demonstrating the cardiovascular system in pericardial effusion. (Same patient as figure 1.) Frontal view shows that the superior vena cava (SVC) and inferior vena cava (IVC) are normal in size, configuration and location. The right atrium (RA), right ventricle (RV) and pulmonary artery (PA) are also normal. Note the pericardial fluid surrounding the right heart structures. Arrow points to the diaphragmatic border of the right ventricle.

Gevalt and Levine [5, 6] have challenged the specificity of Ewart's sign for all pericardial effusions because they found it mainly in rheumatic pericardial effusions. They wondered if the signs were due to an associated rheumatic pneumonitis, a posterior pocket of effusion, or an accompanying pleural effusion. Fenichel and Epstein [7] also found Ewart's sign predominantly in rheumatic

pericardial effusions. Ewart's sign has been elicited in children when there is enlargement of the left ventricle due to either congenital or acquired heart disease.[8] Chapman and Anderson [9] have also reported Ewart's sign in adults with enlarged hearts.

Connor in 1926,[10] quoting the work of Curschmann,[11] advocated the posterior thoracic site for pericardial paracentesis. He reasoned that the left pericardial

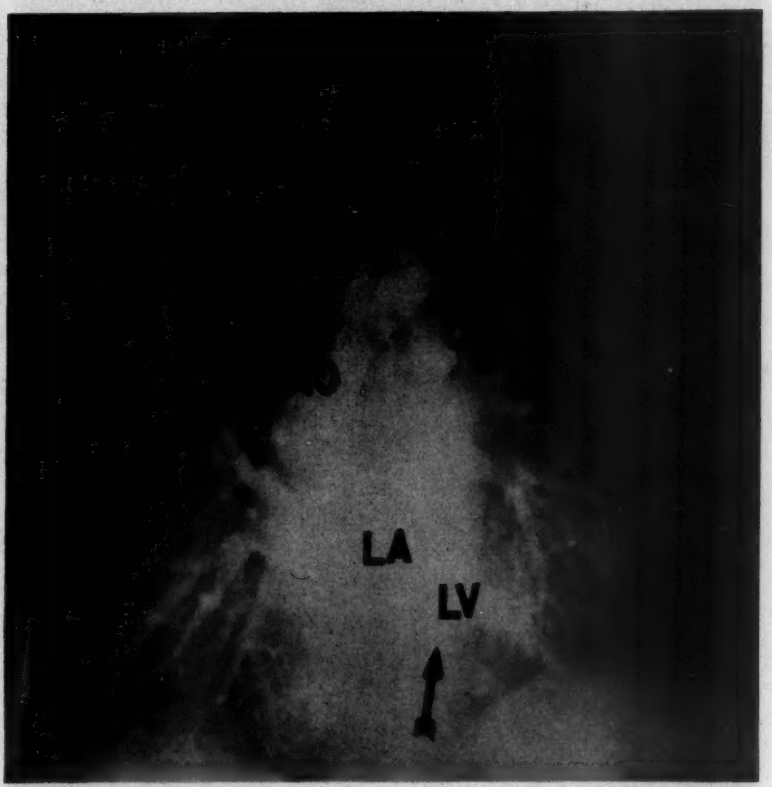

FIG. 2B. The left atrium (LA) with its venous channels is opacified. The left ventricle (LV) and the aorta (AO) are also revealed. Arrow points to the diaphragmatic border of the left ventricle. Again note the fluid surrounding the left heart.

pouch as it became distended by fluid pushed the lung out of the way so that the pericardium actually came into contact with the posterior chest wall, and that the fluid accumulated in this direction caused Ewart's sign. He also argued that the heart was fixed anteriorly and superiorly by the superior vena cava and aorta and by the inferior vena cava below, and therefore could not move backward. Following this paper, the posterior thoracic approach for tapping pericardial fluid became popular.[12, 13] A glance at the lateral angiocardiograms in pericardial effusion, however (figures 2C and D), shows that the heart *does*

move backward, and that the left atrium is *border forming* posteriorly. If pericardial fluid is obtained by the posterior route, it is probably from puncture of the infracardiac pericardial space. For example, Sutton,[13] in discussing the site of needle insertion, stated that in children she preferred the center of the area of bronchophony and bronchial breathing, usually at the level of the eighth to

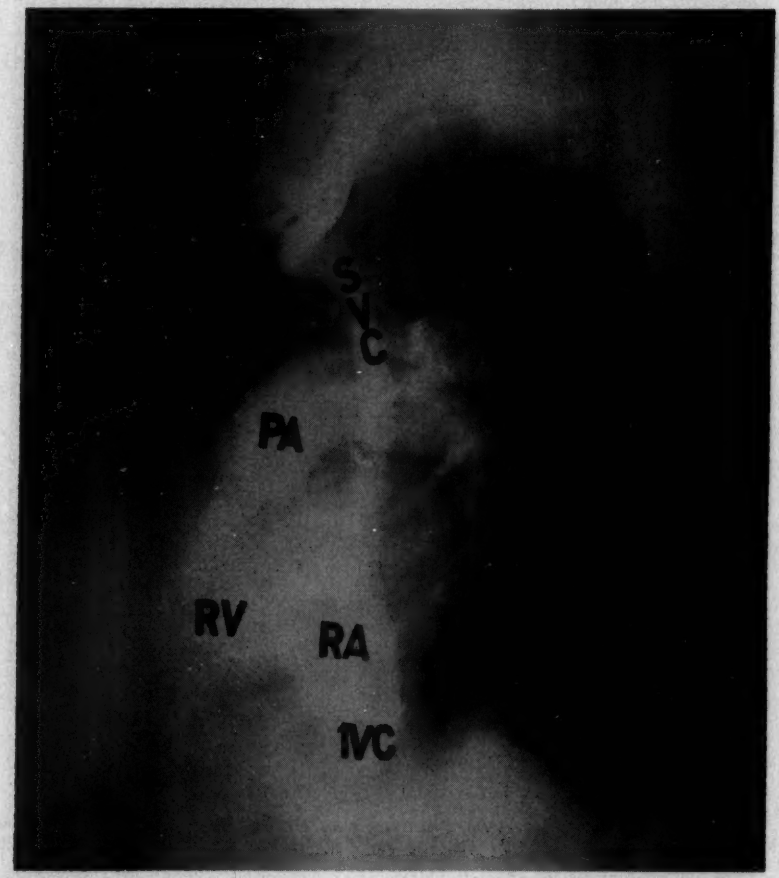

FIG. 2C. Left lateral projection, showing the opacified right heart structures. Note the huge retrosternal and infracardiac pericardial effusion.

eleventh dorsal vertebra. This is obviously low in the thoracic cavity. She also emphasized that the puncture should be nearer the axilla than the spine. A needle inserted in this area probably yields fluid by tapping the distended lateral pericardial pouch.

Williamson [14] and Sauerbruch [15] found that fluid in the pericardium first collected in the region of least resistance, the lower infracardiac pericardial

recesses. Fleischner [16] and Roessler [17] were able to confirm this roentgenographically by demonstrating that in small effusions, although the cardiac shadow was not enlarged, there was a convex bulge of the posterior lower border (best seen in the lateral position) in place of the normally straight or slightly concave

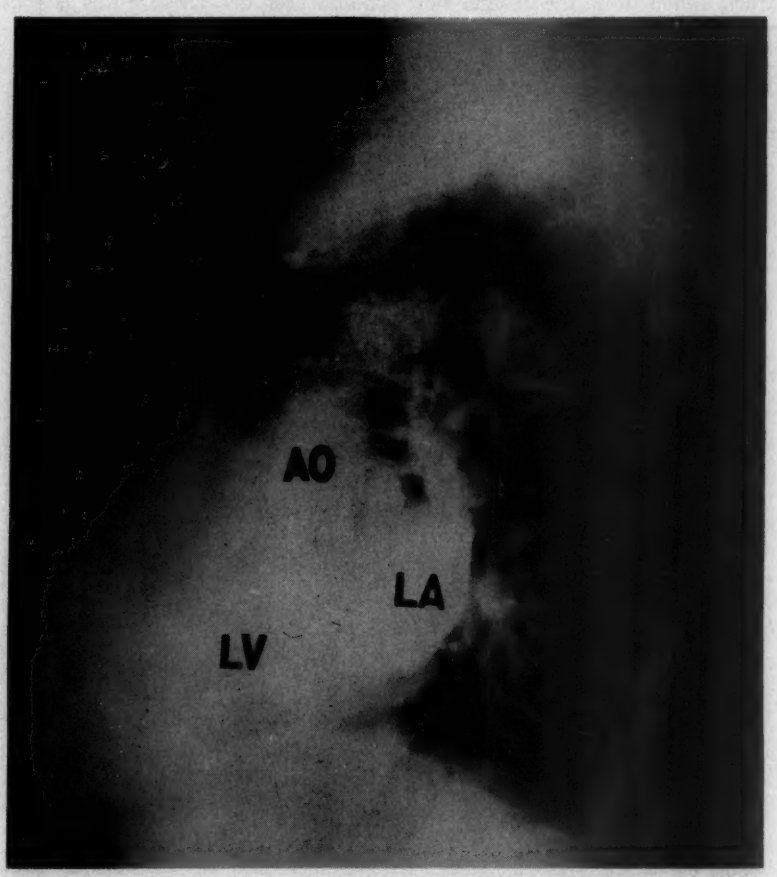

FIG. 2D. Left lateral view of the opacified left heart structures. Note that the left atrium is border-forming; the pericardial effusion surrounds the anterior and diaphragmatic portions of the heart.

contour. It is generally agreed that as fluid in the pericardium increases there is marked change in the configuration of the cardiac silhouette. The transverse diameter increases, the normal arches become obliterated, and the heart shadow becomes globular and later bottle-shaped. This is because the retrosternal pericardial space becomes filled (figures 1B, 2C and D), a sign also described by Golden,[18] and demonstrated in pneumopericardium by Roessler.[17] With massive

effusions the lateral pericardial pouches become markedly distended and may extend far backward (figures 4A and B). In such circumstances, a needle directed low through the left back near the axilla will traverse the lung, puncture the left pericardial recess and reach the effusion. Haziness of the posterior cardiac silhouette in the oblique view has also been described;[19] this is apparently due to the pulsations of the posterior cardiac chambers.

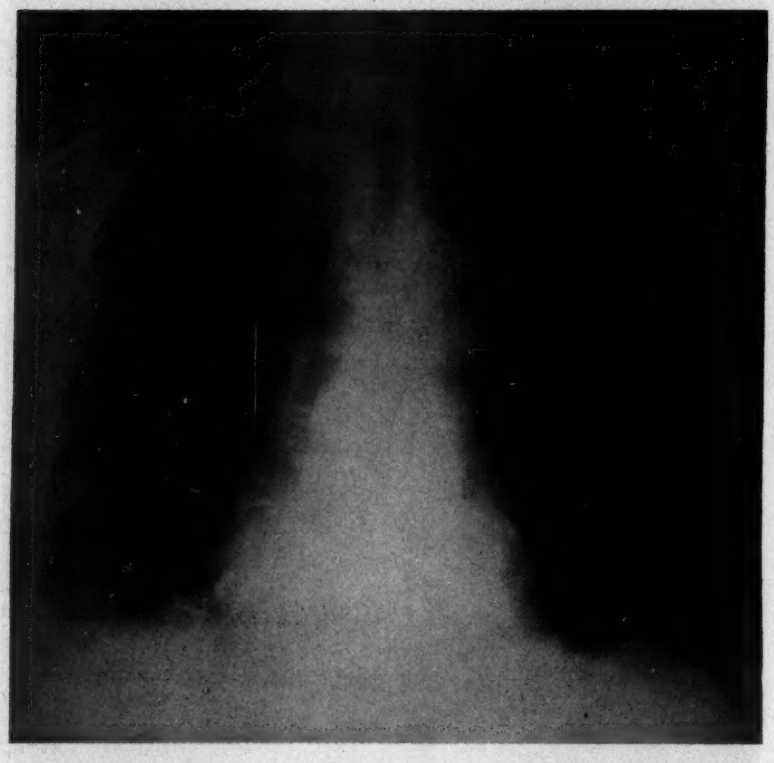

FIG. 3. Postoperative frontal teleroentgenogram (same case as figures 1 and 2), showing the normal cardiac silhouette. The pericardial fluid was nonloculated; following operation, recovery was uneventful.

It would appear that Ewart's explanation is correct that "partial collapse of pulmonary tissue with pressure on the bronchi" in pericardial effusion is responsible for the abnormal physical findings found in the lower back. The posteriorly displaced blood-filled cardiovascular system is certainly capable of compressing the lung. If there is, in addition (figures 4A and B), marked distention of the lateral pericardial pouches, Ewart's sign may indeed be enhanced. When Ewart's sign is absent, it follows that the pericardial effusion is probably small, and not enough backward displacement of the heart has occurred.

In summary, pericardial effusions begin in the infracardiac diaphragmatic portion of the pericardium. As fluid increases, the retrosternal pericardial space is filled. Indeed, this can often be demonstrated by eliciting dullness over the sternum. In pericardial effusions, the heart is surrounded by fluid, except

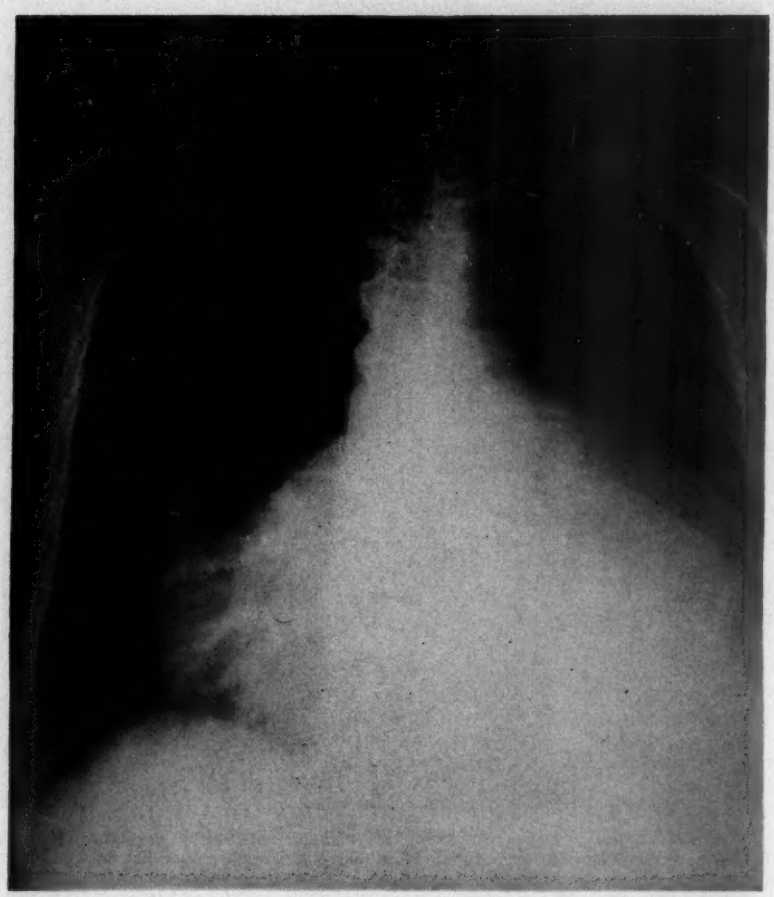

FIG. 4A. Conventional roentgenogram of a 63 year old woman with massive, long-standing pericardial effusion. Frontal projection reveals marked distention of the left lateral pericardial pouch.

posteriorly, where pericardial reflections over the inferior vena cava below, the pulmonary veins, pulmonary artery and aorta above prevent accumulation of fluid. Because of the retrosternal pericardial accumulation, the blood-filled cardiovascular structures are forced backward, compress the lung and bronchi, and are responsible for Ewart's sign.

In massive pericardial effusions, marked distention of the lateral pericardial pouches occurs; they behave like inflated water wings, and cause additional compression, enhancing Ewart's sign. Pericardial paracentesis through the posterior approach when made low in the thorax yields fluid either from the infracardiac

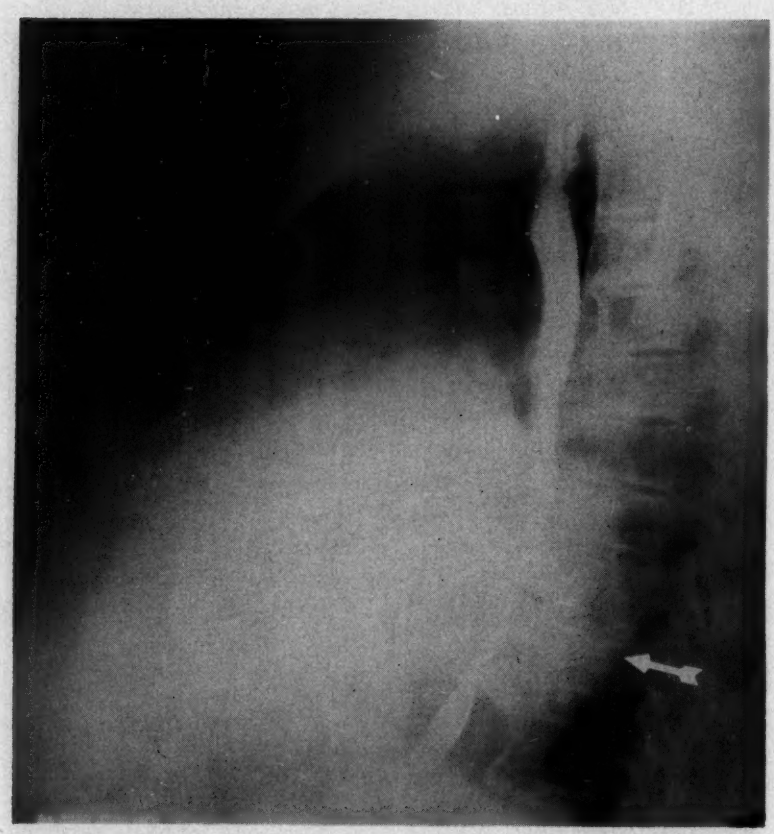

FIG. 4B. Lateral esophagram shows the convex, backwardly displaced retrocardiac structures adjacent to the esophagus. Note the left lateral pericardial pouch (arrow). Ewart's sign is due to compression of lung by the backward displacement of the heart and/or distended lateral pericardial pouches.

pericardial space or from the distended lateral pericardial pouches. To avoid traversing lung, the anterior route in the region of the xiphoid process or apex of the heart is recommended for pericardial paracentesis.

SUMMARIO IN INTERLINGUA

Le uso de technicas angiocardiographic—demonstrate in illustrationes—permitte monstrar que effusiones pericardial comencia initialmente in le portion diaphragmatic

infracardiac del pericardio. Quando le quantitate del fluido cresce, le spatio pericardial retrosternal es plenate. Isto es frequentemente evidentiate per un reducite sonoritate percussive supra le sterno. In effusiones pericardial le corde es circumdate de fluido, excepte posteriormente ubi reflexiones pericardial super le vena cave inferior in basso e le venas pulmonar, le arteria pulmonar, e le aorta in alto preveni le accumulation de fluido. A causa del accumulation pericardial retrosternal, le structuras cardiovascular que es plenate de sanguine es fortiate in retro e comprime le pulmon e le bronchos. Isto es responsabile pro le reducite sonoritate percussive del signo de Ewart.

In massive effusiones pericardial, il occurre un marcate distension del lateral saccos pericardial. Illos se comporta como inflate "alas de aqua" e causa un compression additional. Isto reinfortia le signo de Ewart. In paracentese pericardial con accesso posterior, si effectuate basse in le thorace, le fluido obtenite veni ab le spatio pericardial infracardiac o ab le distendite saccos pericardial lateral. Pro evitar transversar le pulmon, le accesso anterior in le region del xiphoide o del apice del corde es recommendate pro paracenteses pericardial.

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PAROTID ENLARGEMENT IN CIRRHOSIS OF THE LIVER *

By IRVING B. BRICK, M.D., *Washington, D. C.*

IN a short period of time two cases have been observed of cirrhosis of the liver with manifestations of hepatic decompensation, accompanied by bilateral parotid hypertrophy of generous proportions. As the parotid enlargement was readily noted on physical examination, it presented the problem in these two patients of a differential diagnosis of jaundice with parotid enlargement. Since both patients happened to be Negroes, the suspicion of sarcoidosis was immediately entertained, but no other evidences of this disease were found. Furthermore, biopsy of the parotid gland in both cases did not reveal any specific disease, and thus eliminated sarcoidosis or another granulomatous disease as a cause of the bilateral parotid enlargement.

Surprisingly, no paper in the English medical literature of the last 25 years that was reviewed emphasized in the title the relationship between parotid hypertrophy and cirrhosis of the liver. Nor was it mentioned in any of the recent textbooks on either gastroenterology or liver disease, including those by Bockus,[1] Jones,[2] Lichtman,[3] Spellberg,[4] Sherlock[5] and Schiff.[6] Nor did the articles, which are very thorough, by Ratnoff and Patek[7,8] on portal and postnecrotic cirrhosis of the liver, or the careful autopsy studies of 782 cases by Hall, Olsen and Davis,[9] mention the occurrence of bilateral parotid enlargement in cirrhosis.

A thorough scrutiny of the foreign literature produced articles by two groups, one in Italy and the other in France, specifically about the relationship of parotid enlargement and cirrhosis of the liver. Even more surprising was the fact that, although both these authors found the occurrence of parotid enlargement to be quite common in cirrhosis, there was a conspicuous paucity of mention of this finding in the English literature. However, mention of parotid enlargement is found in various papers relating to malnutrition. Because of this interesting and, as far as the English literature is concerned, apparently rare finding, it was deemed appropriate to report these two cases and to review the problems aroused by this combination.

CASE REPORTS

Case 1. A 52 year old Negro male insurance adjuster was admitted to the hospital on July 23, 1956, because of complaints of lower abdominal pain of two months' duration. The patient had also noted weight loss, fatigue and anorexia for the last six months. He had weighed 231 pounds a year before; on admission his weight was 185 pounds. For the last four months he had noted persistent, painless swelling of his face below his ears. In the last two months he had also noted that his eyes were yellow and his urine was dark. There had been no itching and no exposure to toxins, and he had not taken any drugs prior to admission to the hospital. About two months prior to admission the patient had been attacked in another city with a blackjack and been knocked unconscious. His right humerus had been broken and a cast was necessary. Since that attack he had noted chronic lower abdominal pain

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which did not radiate. He gave a history of having drunk at least six highballs a day for the last 22 years, and had continued drinking until two months before. As far as he knew, there had been no exposure to mumps, nor had he had mumps as a child.

Physical examination revealed an alert, coöperative Negro male. Bilateral parotid gland swelling was quite striking; it was nontender and firm, but not stony-hard. Deep palpation did not elicit any pain, and no erythema about the gland was noted. Figure 1 is a photograph of the patient. The sclerae of the eyes were quite yellow.

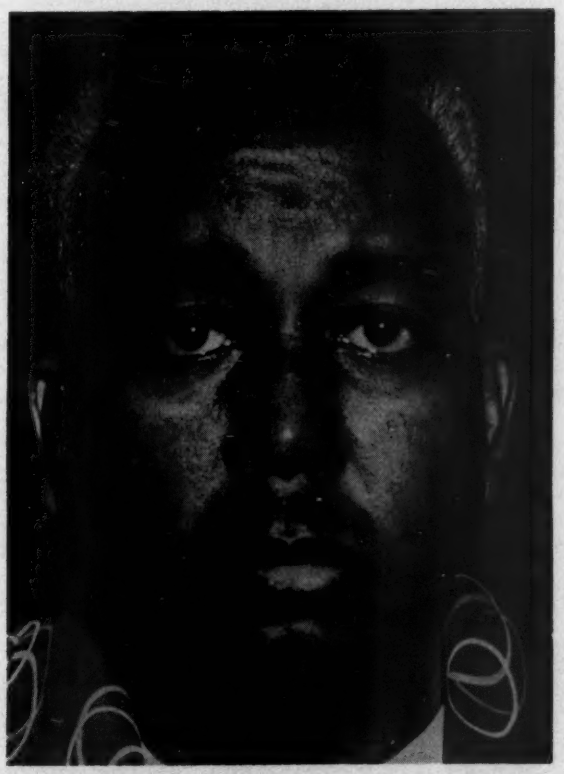

FIG. 1. *Case 1.* Photograph of patient showing bilateral parotid enlargement.

Examination of the lungs and heart was not remarkable. On examination of the abdomen, the liver edge was felt 4 cm. below the right costal margin in the midclavicular line. The spleen was not palpable. No ascites was present, and there was no edema of the lower extremities. Laboratory data included a hematocrit of 33 vol.%. Red blood count was 3,650,000 per cubic millimeter; hemoglobin, 11.2 gm. per 100 c.c. of blood; reticulocyte count, 3%; platelet count, 120,000 per cubic millimeter. White blood cell count was 9,000, with 80% segmented neutrophils, 17% small lymphocytes, 2% monocytes and 1% basophils. On the blood smear the red cells showed slight anisocytosis, with some of the red cells appearing macrocytic. The serologic test for syphilis was negative. The bone marrow was interpreted as

TABLE 1
Laboratory Data on Admission

	Case 1	Case 2
Serum bilirubin (1 Min./Total) (mg. %)	3.1/5.0	3.9/7.1
Serum albumin (Gm. %)	2.3	2.7
Serum globulin (Gm. %)	7.0	4.4
Serum alkaline phosphatase (Bodansky units)	5.6	11.1
Cephalin flocculation (24 hrs./48 hrs.)	3+/4+	3+/3+
Thymol turbidity (Maclagan units)	30	4.3

being a hypocellular preparation with megaloblastic changes in the red cell series and a moderate increase in the plasma cells and reticulum cells. The marrow picture was thought to be consistent with the diagnosis of chronic liver disease. Tests of liver function are shown in table 1. Serum calcium was 11 mg. per 100 c.c., and serum phosphorus was 4 mg. per 100 c.c. A fasting blood sugar was 118 mg. per 100 c.c.; blood urea nitrogen, 10 mg. per 100 c.c.; serum amylase, 74 units (normal in the hospital laboratory). Prothrombin time was 62%, and prothrombin consumption was 48 seconds (control, 52 seconds). Many urobilinogen determinations were performed on two-hour specimens of the urine and the results were uniformly

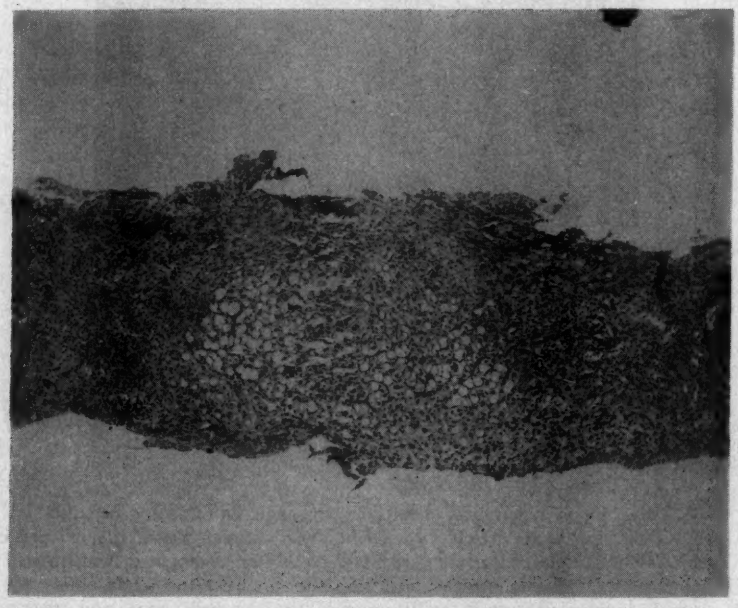

FIG. 2. *Case 1.* Photomicrograph of liver biopsy (× 48) histologically consistent with portal cirrhosis.

high, varying from 2.0 to 7.2 Ehrlich units. A heterophil antigen agglutination test was reported to be 1 to 56. Fourteen days after admission the serum bilirubin was 1.6 mg. per 100 c.c. one minute direct, and 2.1 mg. per 100 c.c. total. At this time the bromsulfalein test (5 mg. per kilogram of body weight) revealed 40% retention at 45 minutes.

An x-ray of the chest showed the lung structure and the mediastinum to be normal. X-ray examination of the parotid areas revealed large, soft tissue masses bilaterally, 8 by 3.5 cm. in size. No calcification could be seen, nor were any calculi in the parotid duct noted. The liver biopsy showed histologic changes consistent with portal cirrhosis of the liver (figure 2). An aspiration biopsy of the right parotid gland revealed normal parotid tissue (figure 3).

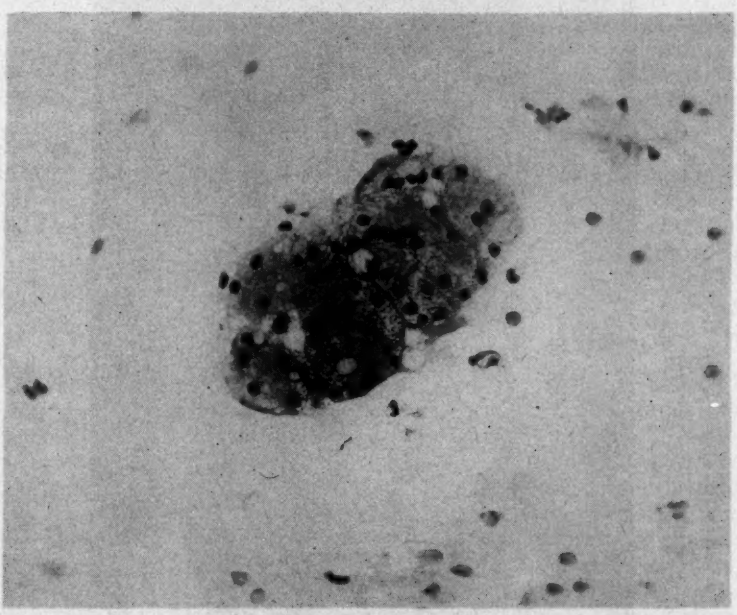

FIG. 3. *Case 1.* Photomicrograph of aspiration biopsy of the parotid gland (× 305). Interpreted as normal parotid gland.

The patient was treated with bed-rest and a nutritious diet containing 60 gm. of proteins daily, and received two transfusions because of his anemia. During his hospital stay he had a febrile course and was given a short course of Aureomycin. His condition improved, and at the time of discharge he was much less jaundiced, and his liver was smaller than on entry. However, there was no change in the size of the parotid glands.

Case 2. A 44 year old Negro female was admitted to the hospital on July 17, 1956, because of the yellow color of her eyes for the last four weeks. The patient was not too well oriented, and the history was believed to be not completely reliable. However, according to her she had not been well for the last six months. At that time generalized weakness accompanied by anorexia and nervousness had been noted. She was treated by her family physician with injections and tablets by mouth. We

learned from this physician that the drugs given were not those ordinarily considered to be hepatotoxic, such as methyltestosterone and chlorpromazine. Six weeks prior to admission the patient had noted chills, fever and sweats, and since that time had had a temperature elevation. Four weeks prior to admission she observed the yellow coloration of her eyeballs, accompanied by dark urine. Edema of the ankles was noted a week prior to admission. She had lost 20 pounds in the six-month period.

FIG. 4. *Case 2.* Photograph of patient.

At the time of admission to the hospital she denied excessive use of alcoholic beverages, but consultation with her family confirmed the suspicion that the patient had been a heavy and persistent user of alcohol in all forms for many years.

Physical examination revealed a dull Negro female of less than average intelligence. Her sclerae were quite icteric. Examination of the heart and lungs was not remarkable. There was quite obvious bilateral parotid enlargement (figure 4). The patient was not aware of this enlargement, nor had she been told about it by her family or friends. The abdomen was quite protuberant, and the liver edge was palpated 11 cm. below the right costal margin in the midclavicular line. Moderate ascites was present, and also moderate pitting edema from the ankles to the knees.

The hematocrit was 28 vol.%; hemoglobin, 8.7 gm. per 100 c.c. The white blood cell count was 19,800 per cubic millimeter, with a marked shift to the left on the smear. The reticulocyte count was 4%. The serologic test for syphilis was negative, as was a Coombs' test. The prothrombin time was 18%, or 27 seconds. Several urobilinogen determinations, using a two-hour urine specimen, were abnormal, varying from 1.3 to 5.7 Ehrlich units. Liver function tests on admission to the hospital are shown in table 1. Chest x-ray was not remarkable. There was no mediastinal widening. Roentgenographic study of the gastrointestinal tract was quite normal. Esophagoscopy revealed moderately large esophageal varices. Treatment, including bed-rest, an adequate diet containing 70 gm. of protein daily, with vitamin supplements, and three 500 c.c. transfusions for her anemia, brought about a marked improvement. She was discharged after two months in the hospital, quite improved, with a total serum bilirubin of 1.4 mg. per 100 c.c. A parotid biopsy was reported to show mild fatty infiltration in otherwise normal parotid tissue. At discharge the parotid enlargement was slightly less prominent than on admission, but was still easily noted.

Discussion

Both of these cases showed marked evidences by clinical and laboratory findings of decompensated chronic liver disease. The unique feature of bilateral parotid enlargement in these jaundiced patients brought up the matter of differential diagnosis, and such entities as parotitis, sarcoidosis, Mikulicz's disease, lymphomas and various tumors as well as infections were considered. However, the biopsy in both cases was not specific for any such entity, and it was considered that the parotid enlargement was part of the generalized effects of cirrhosis of the liver.

Parotid Enlargement in Malnutrition: In the literature on the relationship of parotid enlargement and cirrhosis, parotid enlargement is mentioned by various authors in studying malnutrition. Since malnutrition is frequently found in the background of the cirrhotic patient who is an alcoholic, it was interesting to note the comments about parotid enlargement in various diseases of malnutrition. Kenawy [10] studied 100 cases of painless parotid swelling among agricultural workers along the upper Nile in Egypt. Most of these patients were unaware that they had any enlargement of the parotid gland. The diet in this group of patients was limited, and comprised primarily maize, cheese and onions. Histologically, the parotid gland in this group showed an increase of the ducts and ductules, with crowding of the acini, which was interpreted as representing a picture of hyperplasia without other abnormal findings. A summary of these 100 cases shows that 65 had pellagra, 10 had diabetes, six had cirrhosis, and four had anemia associated with ancylostomiasis.

Gillman and Gillman [11] discussed the reactions of the salivary gland in malnutrition, particularly in cases of pellagra. They believed that these glands are affected primarily by the changes evidenced in the saliva. Ptyalism was a frequent symptom in pellagra. The salivary glands were seriously affected by malnutrition. They stated that enlarged parotids are often seen in both pellagrous and nonpellagrous malnourished Africans. Examination of tissue from these enlarged parotid glands showed enlargement of the individual tubules or acini. The acini appeared to be crowded with secretory granules. It was the opinion of the Gillmans that the enlargement of the parotid glands was due mainly to an increase in the size of the individual cells. In some hypertrophied

parotid glands there was a great accumulation of fat, but they believed that the increase in size was due primarily to the increase in the acinar tissue. No mention is made by them of the occurrence of parotid enlargement in patients with cirrhosis, although it can be assumed that among this malnourished African group that they studied, nutritional types of cirrhosis were not uncommon.

After a scholarly study of undernutrition in Germany at the end of World War II, a large group of English investigators issued a special report on this subject. In this study of malnutrition there was a chapter on the enlargement of the parotid glands by McCance, Dean and Barrett.[12] These workers reviewed the subject of enlargement of parotid glands in malnutrition, and incidentally mentioned the fact that there had been reports of isolated cases of enlargement of the parotid glands in many prisoner-of-war camps, along with gynecomastia. However, in none of their studies was enlargement of the breasts related with any degree of regularity to enlarged parotid glands. In some instances parotid enlargement was also observed when repatriated prisoners were putting on weight as a result of good nutrition. Actually, at this time the repatriated prisoners were eating enormous quantities of food, and it was believed that the parotid enlargement was a result of the improvement in their weight and health. Davies,[13] who has done a great deal of work on kwashiorkor, noted that in this group of patients swollen parotids were among the first signs of recovery when the patients were fed. In discussing the possible relationship between gynecomastia and parotid enlargement, the authors stated: "An excess of these hormones (estrogens) can hardly explain the enlargement of salivary glands where there is no development of the breasts, but the liver may yet turn out to be involved in the parotid enlargements, for Lang described a post-mortem in which true parenchymatous hypertrophy of parotids was associated with atrophic cirrhosis of the liver." The authors also pointed out that the enlargement had been attributed to interstitial edema, fatty infiltration, "work" hypertrophy and parenchymatous hypertrophy, and an increase in the size of the individual cells. It is also of interest that some workers in the field of malnutrition have reported atrophy of the salivary glands in undernourishment.

McCance, Dean and Barrett [12] stated that enlarged parotid glands were a common sight in the German men who had recently been repatriated from Russia. On their return to Germany these men were thin, but on feeding they put on weight rapidly, their cheeks becoming fatter and their parotid glands beginning to swell. This made their ears stick out in a very characteristic way. The enlargement of the parotid always followed the return to a generous diet. There were no evidences of gynecomastia in the patients observed. Among undernourished civilians in the same population, enlarged parotid glands were not noted. Swellings noted were soft, not invariably symmetric, and painless. There was no evidence of inflammation around the glands. Tissue was obtained from a patient who died of acute infectious endocarditis after an illness of only eight or nine days and who had had very enlarged parotids in life. No definite histologic abnormality was observed, and there was no inflammatory infiltration or fibrosis. The amount of adipose tissue was within normal limits, although the individual fat cells seemed rather large. It was also believed, but this was not conclusive, that the individual acini were enlarged. The impression was that the swelling of the parotid glands was part of the response to overfeeding after a prolonged period of undernutrition. Thus the enlargements of the paro-

tid glands could be regarded as a work hypertrophy. To summarize this study, it can be said that enlarged parotid glands were seen in repatriated prisoners-of-war who were gaining weight rapidly. Swellings were not tender or inflamed, and a postmortem examination of one gland showed the tissue to be essentially normal. The men who had bilateral parotid enlargement did not have enlarged breasts.

Another survey on this matter was conducted recently by Sandstead, Koehn and Sessions.[14] In a study of individuals in an American institution they found that parotid enlargements were frequent among Indians, and much more frequent among Negroes than among white patients. In another survey of patients in three Indian hospitals, it was noted that 20 (or 12%) of 165 American Indian patients had parotid enlargement. This paper also notes that when hospital records were reviewed to ascertain whether the parotid enlargement had been previously seen, no information relative to the parotid gland could be obtained. Undoubtedly, this finding is overlooked in general hospitals on physical examination, and therefore a review of hospital records would not be very accurate in revealing such cases among previously seen cases of hepatic cirrhosis. In none of the cases in this survey in which bilateral parotid enlargement was noted was there gynecomastia. Histologic study of the parotid tissue did not reveal any common pathologic changes to explain the clinical finding of parotid gland hypertrophy. In two other groups of patients, the second group being in an Asian population in which parotid enlargement was found in 369 (or 11.6%) of 3,168 persons examined, fatty infiltration was noted histologically but was not believed to be sufficient to explain the enlargement of the parotid gland. In some of the studies of the histologic sections, the lobules appeared to show enlargement of the individual cells, which had previously been mentioned.[11, 12] The authors believed that enlargement of the parotid glands was a manifestation of chronic and possibly a severe form of malnutrition. The dietary factors were not identified, but the condition occurred most frequently among subjects who presented multiple signs of deficiency disease, such as underweight, pellagrous pigmentation of the hands and face, angular cheilosis, calf muscle tenderness, anemia and hypoproteinemia. In this study only the total plasma protein determinations were presented.

In these studies of malnutrition it would therefore appear that enlargement of the parotid gland, when specifically searched for, was present not infrequently. There appears to be no specific explanation for this enlargement, but, as is often the case in alcoholic cirrhosis, there were evidences of malnutrition. It is interesting that hypoproteinemia was mentioned as a possible factor in enlargement of the parotid glands, inasmuch as this is a common finding in patients with cirrhosis. Hypoalbuminemia was found in the two patients presented in this report. There was apparently no correlation with cases of gynecomastia, also sometimes seen in malnutrition. The observation that, in repatriated German prisoners-of-war, refeeding of nutritional diets resulted in the appearance of parotid enlargement is also analogous to the gynecomastia reported on refeeding of repatriated prisoners-of-war from Japan. Apparently, too, there was no specific histologic pattern in the pathologic study of the enlarged parotid glands. Many types of histologic findings were mentioned, including fatty infiltration and increase in size of the individual cells, but nothing distinctly abnormal can be ascribed to the tissue of the enlarged parotid glands. Apparently in none of

these studies was there any specific attempt to correlate the enlarged parotid gland with liver function tests, or with the possible diagnosis of cirrhosis. However, the finding of bilateral parotid enlargement in malnutrition is conspicuous enough to attempt a correlation with the findings in alcoholic cirrhosis, in which malnutrition is certainly often present.

Cirrhosis of the Liver and Parotid Enlargement: Because of the absence in the English literature of any mention of the relationship between parotid enlargement and cirrhosis, and because of the frequency with which this finding was noted in cirrhosis of the liver by two groups of workers, one in Italy and the other in France, it was deemed advisable to have an exact translation of the three definitive articles [15, 16, 17] by this group of investigators.* In the first paper on the subject, Sposito [15] stated that he had been observing enlargement of the parotid gland in cirrhosis of the liver for many years. Although in normal people the parotid glands cannot be palpated, he had noted enlargement of the parotid glands by palpation in 24 of 28 cases of cirrhosis, 12 confirmed by autopsy. In 15 of the 24 cases the enlargement of the parotid glands was bilateral, whereas in nine the swelling was more in evidence on one side, usually the right. A figure of the incidence of enlargement of parotid glands in cirrhosis of the liver of 86% was given. The author stated that in some cases parotid enlargement was barely palpable, whereas in other cases it was quite deforming. The skin over the glands was mobile, and no pain was noted by the patient. There was no evidence of infiltration. Biopsies of the parotid gland were obtained in seven cases, and in all seven there was hyperplasia of the glandular parenchyma with some increase in connective tissue, particularly interlobar connective tissue. In only a few cases was fatty infiltration seen. The author pointed out that, in reviewing the medical literature, he could find no statement recording this hypertrophy of the parotid glands in cirrhosis of the liver. In the textbook on pathology by Henke and Lubarsch, Rössle mentioned enlargement of the parotid gland in an obese male who had cirrhosis. However, it was felt that the enlargement of the parotid glands was related more to the excessive intake of food than to the cirrhosis.

In another paper, Sposito and Cheli [16] referred to the previous paper and presented 10 cases of parotid enlargement from whom biopsies of the parotid glands had been obtained. Of these 10 cases, six had portal cirrhosis, one had cirrhosis caused by chronic brucellosis, one had sprue, one diabetes mellitus, and one was a case of parotid enlargement in a patient with syphilis and congestive heart failure. The histologic study of these parotid biopsies again confirmed the previous histologic findings of glandular hyperplasia with a modest increase of fatty infiltration. It was of interest that in the other cases the histologic findings were the same in the parotid glands as the findings noted in cases of cirrhosis. In attempting to explain the parotid enlargement in cirrhosis the authors indicated that, since the enlargement of parotid glands was also noted in sprue and diabetes, and since the histologic findings of the parotid glands are the same in the cirrhosis as in the sprue and diabetic patients, pancreatic sclerosis can be considered to be a common denominator. The authors concluded that the clinical manifestations of parotid hyperplasia raised the suspicion that a chronic

* The translations of these three articles were made by Mr. M. A. Kravanja, National Library of Medicine (formerly U. S. Armed Forces Medical Library), Washington, D. C.

hepatopancreatic disease may be present to explain the frequency of the parotid swelling in cirrhosis of the liver.

From the Clinic and Laboratory of Tropical Medicine of the Medical School of Bordeaux, France, Bonnin, Moretti and Geyer [17] expressed surprise that the swelling of the parotid glands occurring in cirrhosis of the liver and also in the precirrhotic alcoholic stages had not attracted more attention. In research on malnutrition syndromes in the tropics, they found that the incidence of parotid enlargements, as well as atrophy of the parotid, was quite high. Inasmuch as cirrhosis of the liver in the tropics was often present in severe nutritional disorders, it was thought appropriate to study the parotid glands in the cirrhosis seen in France. To the surprise of these workers, hypertrophy of the parotid glands was found so regularly that it appeared to be a constant manifestation of alcoholic cirrhosis. In their patients this parotid hypertrophy was found both in alcoholic fatty cirrhosis and in cirrhosis without ascites. It was also found in alcoholics who had no apparent sign of cirrhosis. These authors believed that the swelling of the parotids began early in the disease, even though its beginning was not well defined, due to the fact that the swelling of the parotids was quite indolent. Men and women with cirrhosis had this enlargement of the parotid glands equally. It appeared most often at about the fiftieth year, but was also found in younger patients, especially in alcoholics. Patients with parotid enlargement did not complain of pain and had no temperature elevation, and the mouth was normally moist. Most of these patients paid no attention to this abnormality of their faces. Although the enlargement of the parotid gland was usually bilateral and symmetric, it may also be greater on one side, usually the right. In a study of 173 patients with confirmed cirrhosis, with or without ascites, and with or without jaundice or edema, 80% had parotid enlargement.

In differential diagnosis, the authors stated that there was no difficulty in the cases where there was bilateral indolent swelling of the parotid glands without fever, and with concomitant evidence of cirrhosis or alcoholism. Various diagnoses, such as mumps, Mikulicz's disease or sarcoidosis, were more theoretic than practical. Only when the patient was obese was there difficulty in differential diagnosis, since enlargement of the parotid glands is more apt to occur in the obese patient than in the patient of normal weight. In studying the biopsies of the parotid glands in these patients, the authors found that the parenchyma was similar to that of a mucus gland, with a limpid foamy mucus cytoplasm. The authors call this aquiparous aspect of the parotid glands unique, and even characteristic of the parotid glands of patients with cirrhosis of the liver. Adjacent to this finding was what was interpreted by the authors as a marked overactivity of the secretory cycle in the cell. The glandular cells were markedly hypertrophied. The fatty tissue, usually present in normal proportions, was occasionally increased. Histologically, therefore, the authors believed that parotid enlargement in cirrhosis of the liver demonstrated manifestations of hyperactivity, hypertrophy and hyperplasia of the cellular elements. These authors also studied parotid secretions by catheterization of Stensen's duct. Studying the amylolytic activity of parotid secretion before breakfast, these authors found the normal activity level to range from 2,000 to 4,000 Wohlgemuth's units, but in the patients with cirrhosis and parotid enlargements the levels ranged from 6,000 to 8,000 Wohlgemuth's units.

The authors discussed the various instances of parotid enlargement in mal-

nutrition syndromes without evident hepatic involvement. It was their belief that malnutrition was responsible for the various hypertrophies of the parotid glands. After discussing the various malnutritional syndromes with parotid enlargements seen in various parts of the world, particularly in the tropics, they concluded that the only factor common to all these observations in which the parotid gland hypertrophy is present is the nutritional disorder, without regard to the fact that malnutrition may or may not have caused cirrhosis in these patients. It was their belief that the enlargement of the parotid glands in alcoholic cirrhosis offered general proof that cirrhosis went well beyond the liver and gastrointestinal tract in its manifestations, and also offered an additional analogy of alcoholic cirrhosis to malnutritional syndromes, with or without cirrhosis.

Discussion

One surprising aspect of these reports by two groups of observers in Italy and France was the frequency with which parotid enlargement was found in cases of cirrhosis. Inasmuch as a high proportion of the cases presented was confirmed by biopsies of the liver as well as of the parotid glands, there seems no reason to doubt the diagnosis of cirrhosis in these cases. The absence of any mention of these findings in the English literature relating to cirrhosis is difficult to understand. The author of this paper can recall cases where the plump appearance of the face of several patients with cirrhosis was remarked upon more in passing than otherwise. It seems that in many cases of cirrhosis the parotid region has not been carefully examined. In the two cases presented in this paper the parotid enlargement was so obvious it could not be missed. However, it is easy to understand how lesser degrees of such enlargement could be overlooked on physical examination. Furthermore, routine palpation of the parotid area is not usually done in most general physical examinations. Possibly this explains the high incidence reported by the two groups of workers mentioned with reference to parotid enlargement, since they set about specifically searching for this sign. Normally, the parotid gland cannot be palpated, but minor degrees of enlargement may well be palpable if the gland is assiduously searched for. As was pointed out previously, Sandstead, Koehn and Sessions,[14] in reviewing the physical examination records on patients in mental institutions, found no mention of enlargement of the parotid glands, whereas actually it was not infrequent.

In describing the facies of patients with cirrhosis of the liver, the standard textbooks on diseases of the liver make absolutely no mention of the parotid gland or of parotid enlargement. It is not easy to understand why this relationship has not been commented upon in the English literature, nor is it easy to understand the absence of reports of this physical finding in cirrhosis, inasmuch as parotid enlargement has been reported many times in various malnutritional diseases and syndromes. Furthermore, in the average cirrhotic population in the United States, approximately 70 to 80% of the patients are chronic alcoholics, whose malnutritional problems are well known. Hypoproteinemia was listed as one of the possible factors in malnutrition causing parotid enlargement, and it is interesting that in the two cases here presented hypoalbuminemia was quite marked. Nothing notable was found histologically in the parotid biopsies of our two patients. This is consistent with much of the previous literature on histologic findings in parotid enlargement in malnutrition. It is difficult to esti-

mate enlargement of individual acini, or functional activity on the basis of biopsy specimens.

There were no overt physical or laboratory findings referable to pancreatic disease in our patients. Neither had diabetes mellitus, and the serum amylase level in one patient was within normal limits. However, thorough pancreatic function studies, with study of the pancreatic secretion, were not performed. Inasmuch as the European observers felt that some relationship between involvement of the pancreas in cirrhosis of the liver and the parotid enlargement was possible, it is interesting to note a study of pancreatic lesions associated with cirrhosis of the liver by Stinson, Baggenstoss and Morlock.[18] The histologic findings in the pancreas of 75 patients with cirrhosis of the liver were studied. In 29 of these 75 there was a history of excessive use of alcohol. The histologic variations in these cases were compared with those observed in sections of the pancreas from 75 control patients, in whom no cirrhosis or other hepatic lesions were present. The authors found some degree of inflammatory reaction, either active or healed, in the pancreas of 72 of the 75 subjects with cirrhosis. Varying degrees of pancreatitis, characterized by interstitial infiltration with lymphocytes or polymorphonuclear cells, were found in 51 of the 75 cases of cirrhosis. The involvement was minimal in 35, moderate in 11, and severe in five. In 59 of the 75 cases fibrosis alone, concurrent with some other evidence of injury, was found. In small groups of patients, focal necrosis and calcification were also found. However, the authors believed that in most instances neither the character nor the extent of the pancreatic lesions indicated that they played any role in the pathogenesis of the cirrhosis. It was suggested that the factors responsible for the cirrhosis may also have been responsible for the pancreatic injury. The authors believed it to be doubtful that the degree of pancreatic involvement would have been sufficient to cause any measurable alterations in the functional efficiency of the pancreas. The role of alcoholism in the pathogenesis of pancreatic lesions may not be so widely accepted as it is in the development of cirrhosis, but, according to the authors, it cannot be ignored. However, it would appear from the evidence with reference to pancreatic lesions that it would be difficult to explain the parotid enlargement in cirrhosis on this basis. It is the opinion of the present writer that the physiologic explanation for parotid enlargement in cirrhosis of the liver is yet to be found.

Summary

1. Two cases of bilateral parotid enlargement in patients with cirrhosis of the liver are presented.

2. In the experience of American and English workers, the incidence of this relationship has apparently been minimal. However, it has been reported by workers in Italy and France as occurring with surprising frequency.

3. The relationship of parotid enlargement to malnutritional states has been discussed.

4. Biopsy study of the parotid glands in these cases was not abnormal. The results were valuable in the differential diagnosis from other causes of parotid enlargement.

5. The relationship between pancreatic lesions in patients with cirrhosis and the parotid enlargement is discussed.

6. The cause of the parotid enlargement in patients with cirrhosis of the liver is not known at present. Its true incidence can be ascertained only if enlargement of the parotid glands in patients with cirrhosis is routinely searched for.

Addendum

Two papers on this subject have appeared since the preparation of this manuscript. The first [19] presents 16 cases in which there was parotid swelling accompanying chronic alcoholism and liver disease. Portal cirrhosis was found histologically in seven of the eight patients on whom liver biopsy was performed. The other case demonstrated fatty metamorphosis. No parotid gland biopsies were performed. The authors concluded that their study lent support to the claims in the European literature that asymptomatic enlargement of the parotid glands was frequently found in patients with chronic alcoholism, most of whom have cirrhosis.

The second paper [20] presents six cases of enlargement of the parotid glands in association with liver disease. Moderate obesity was also present, together with arterial hypertension in three cases and an impaired glucose tolerance in three. In four of the cases parotid biopsies were performed and mild to marked fatty infiltration of the parotid gland was noted. The authors felt that the parotid enlargement seemed to have much the same significance as does a fatty liver, pointing to disturbed nutrition or metabolism but not defining the disturbance. In both studies, as well as in the present one, the parotid enlargement caused no symptoms and, indeed, the patients were usually unaware of the condition.

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Summario in Interlingua

Iste reporto presenta duo casos de cirrhosis del hepate accompaniate de bilateral hypertrophia parotidic. Le relation inter le hypertrophia e le cirrhosis es discutite. Es interessante notar que le litteratura de lingua anglese del passate 25 annos, incluse recente manuales, non mentiona ille combination. Del altere latere, le litteratura francese e italian contine mentiones del observation de allargamento parotidic in association con cirrhosis hepatic. In ambe le casos del presente reporto il habeva signos definite de discompensation de chronic morbo hepatic. Le ration pro le hypertrophia del glandulas parotidic non es facile a establir. Es discutite le relation inter allargamento parotidic e malnutrition, le qual ha essite notate in multe partes del mundo. Nulle elemento specific del dieta pare esser responsabile pro le allargamento. Tamen, il es un facto que allargamento parotidic non es incommun in gruppos de patientes qui suffre de malnutrition. Le studio histologic del glandula parotidic in casos de malnutrition non es specific. Isto valeva etiam in le duo casos del presente reporto. Le biopsia del glandulas parotidic non revelava un specific configuration histologic. Le presentia concomitante de morbo pancreatic ha essite postulate como un possibile factor etiologic, sed un scrutinio meticulose del factos non supporta ille hypothese. Sin dubita, le occurrentia de allargamento parotidic in cirrhosis es plus commun que lo que ha essite reportate in le passato. Il es a expectar que iste assertion trovarea su corroboration in le exacte examine del glandulas parotidic de patientes con cirrhosis del hepate. Al tempore presente le causa de allargamento parotidic in cirrhosis hepatic non es cognoscite.

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BACTEREMIA CAUSED BY *MIMA POLYMORPHA*: REPORT OF A CASE *

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IN recent years bacteria from the tribe Mimeae have been cultured from patients with a variety of lesions. This tribe, which is comprised of three genera

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—Mima, Herellea and Colloides—was named and described by DeBord in 1939.[1] In this paper he observed that the tribe Mimeae (mimic) resembles the genus Neisseria in its morphologic characteristics. Their features include pleomorphism, with predominance of diplococci on solid media, and filaments, rods and cocci in liquid media. There are also encapsulation, gram-negativity with some retention of positiveness, and certain carbohydrate fermentation patterns which vary among the three genera.

A case of bacteremia in which *Mima polymorpha* was isolated from the blood stream is described.

Case Report

A 33 year old single white female was admitted to Bridgeport Hospital with a history of sore neck, fever and chills for two weeks. Physical examination revealed a well developed and well nourished, febrile, acutely ill female. Temperature was 101° F. rectally; pulse rate, 112; respiratory rate, 22. The thyroid gland was bilaterally and symmetrically enlarged, firm, warm and very tender. The pain was exaggerated by swallowing. Otherwise, except for a hot, flushed skin, the physical findings were not remarkable. The admission white blood cell count was 11,800, with 82% polymorphonuclear cells; three days later it was 12,600, with 75% polymorphonuclear cells. After stool and blood cultures were obtained, procaine penicillin and Terramycin were begun on the day of admission. The patient remained febrile for six days, with the temperature returning to normal after the sixth day. A level of 104° F. rectally was reached on the first, third and fourth days. A blood culture taken on the day of admission prior to onset of therapy revealed a growth of nonlactose fermenting, gram-negative rods which was identified, in the State Laboratory at Hartford, as *Mima polymorpha*. The remainder of the laboratory data, including the various agglutination tests, stool cultures, etc., was not unusual. Concomitant with the decline in temperature, the pain, tenderness and much of the thyroid swelling subsided.

Comment

The Mimeae tribe of organisms has been isolated from a number of both normal and pathologic conditions. Cultures from children with normal and abnormal vaginal and conjunctival secretions produced this organism in a large percentage of cases.[2, 3] In 1945 Deacon [4] reported 19 cases of human infection with the Mimeae tribe, some cultured from resistant cases of gonorrhea-like infection and others from cerebrospinal fluid after head injury. A case of *Mima polymorpha* meningitis, reported by DeBord [5] in 1948, apparently responded to treatment with sulfanilamide. Cases of bacteremia involving this organism were reported by Faust and Hood [6] in 1949 and by Pike [7] and associates in 1951. The positive blood culture in the latter case occurred in a patient with subacute bacterial endocarditis and responded to oxytetracycline. Sorrell and White [8] recorded a case of acute bacterial endocarditis with an organism which appeared to be a variant of the genus Herellea, tribe Mimeae, in which the prostate may have been the focus of infection for the bacteremia. Schuldberg [9] obtained organisms resembling *Neisseria meningitidis* on an antemortem smear taken from a skin lesion in a baby with meningitis. However, *M. polymorpha* was isolated from the meninges at autopsy. Twenty-four strains of organisms of the tribe Mimeae were isolated during the course of a year from the upper respiratory

and urinary tracts by Scott and Mahoney.[10] Resistance to penicillin, streptomycin and chloramphenicol was noted in almost all strains, but many were sensitive to oxytetracycline and chlortetracycline. Townsend and co-workers [11] reported two cases of infection with *M. polymorpha* as a causative agent in cerebral meningitis (Waterhouse-Friderichsen syndrome), one with autopsy findings and one with recovery after treatment with sulfadiazine and penicillin. Brooks and Sanders,[12] in studying the antibiotic sensitivity of six cultures, found variable sensitivity and frequent resistance to the antibiotics in common use. A case of healed bacterial endocarditis due to an organism belonging to the tribe Mimeae was recently described by Minzter.[13]

In the present case, *M. polymorpha* produced a blood stream infection. Whether this organism was responsible also for the tender and enlarged thyroid gland (thyroiditis) cannot be definitely stated. Sensitivity tests were unfortunately not done, but the patient nevertheless responded to the antibiotic therapy. However, because of the variability of sensitivity and the alarming degree of resistance to the various antibiotics in most cases, it is essential that sensitivity studies be done in each case in which this organism is isolated. Of importance also is the differentiation of the Mimeae tribe of organisms from members of the genus Neisseria, because of the difference in sensitivity findings and, consequently, in therapy.

Summary

1. A case of bacteremia caused by *Mima polymorpha* is described.

2. The literature is briefly reviewed, and it is noted that this organism has been isolated from a variety of both normal and pathologic conditions.

3. Previous reports have stressed the varying sensitivity of members of the Mimeae tribe to the common antibiotics, and also their close morphologic resemblance to members of the genus Neisseria.

Summario in Interlingua

Es discutite un caso de infection del circulation de sanguine per le organismo *Mima polymorpha*. Le patiente esseva un femina de racia blanc de 33 annos de etate qui se presentava con alte grados de febre, mal de gurgite, frigor, e signos de thyroiditis acute. Le culturation de sanguine revelava *M. polymorpha*, e le patiente se restabliva post therapia a penicillina e terramycina. Non es cognoscite le qual del antibioticos effectuava le curation, proque tests de sensibilitate non esseva executate.

Organismos pertinente al tribo del mimeas ha essite isolate ab individuos in varie conditiones normal e pathologic, incluse meningitis, conjunctivitis, vaginitis, endocarditis, e infectiones del vias urinari. Illos es baculiforme, non-fermentantes de lactosa, e negative al Gram. Illos varia in lor sensibilitate, e il ha essite trovate que illos possede un grado alarmante de resistentia al varie antibioticos. Resistentia a penicillina, streptomycina, e chloramphenicol ha essite notate frequentemente. Del altere latere, le organismo se ha monstrate a vices sensibile a oxytetracyclina e chlortetracyclina.

Le differentiation ab le gruppo del neisserias es sublineate a causa del similitude morphologic. Viste que iste duo gruppos differe in lor sensibilitate a antibioticos, un exacte differentiation es necessari pro seliger le correcte therapia.

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CUTANEOUS LYMPHOBLASTOMA: A CASE OF RETICULUM CELL SARCOMA WITH PROMINENT SKIN MANIFESTATIONS AND A BRIEF BUT DRAMATIC REMISSION WITH PREDNISONE THERAPY *

By G. E. Gorsuch, Lieutenant (MC) USN, *San Diego, California*

A discussion of the cutaneous lymphoblastomas traditionally includes not only the primary and secondary cutaneous manifestations of the lymphomas but also those of the various types of leukemia cutis (myelogenous, lymphatic, monocytic and their subleukemic forms), and mycosis fungoides. These diseases are closely related and have similar cutaneous manifestations.[1] Up to 40% of patients with a lymphoblastoma will show cutaneous signs during the course of their disease. Most of these manifestations are nonspecific, and include every known type of skin lesion, whether generalized or local.[2, 3] The specific cutaneous lesions resulting from direct and frequently multiple neoplastic infiltrations into the skin are more unusual.

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Generalized cutaneous reticulum cell sarcoma is not common. Fifteen cases of reticulum cell sarcoma with major or multiple specific skin lesions have been reported in the world literature since 1942. Most of these cases are in foreign dermatologic papers.

In the treatment of reticulum cell sarcomas, remissions have been reported with the use of nitrogen mustard [4] and x-ray therapy.[5] Unfortunately, however, reticulum cell sarcoma in all forms is apt to recur, and the ultimate prognosis is unfavorable. Stout, reporting in 1942 on 89 cases of reticulum cell sarcoma, found that only 12% of all patients with this disease survived as long as five years.[6]

This case of reticulum cell sarcoma with generalized discrete cutaneous nodules demonstrated a brief remission with prednisone therapy.

Case Report

This 63 year old white male was admitted to the U. S. Naval Hospital, San Diego, California, on July 5, 1956, with a chief complaint of "skin spots." He had apparently been in good health until four weeks prior to admission, when he noticed a raised red spot on his upper left chest and one on the right side of his face. He was referred to a private physician, who did a skin biopsy which reportedly showed a reticulum cell sarcoma. One week later, and three weeks prior to admission, spray x-ray therapy was begun. The patient noted that after three treatments his lesions disappeared but more appeared elsewhere on the skin, and this continued throughout his 15-treatment x-ray course. His last x-ray therapy was 10 days prior to admission. Lesions continued to appear. In the next 10 days, his spots increased in size and number "fast and furiously." The patient reported to the Naval Hospital for evaluation and treatment. Except for a six pound weight loss he had no other symptoms. Review of systems was negative.

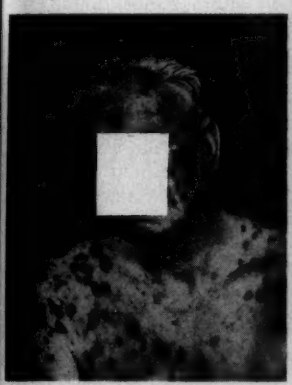

Fig. 1.

Fig. 2.

Fig. 3.

Skin manifestations in reticulum cell sarcoma before the use of prednisone therapy.

Physical examination on admission revealed an obese but well developed and well nourished white male who appeared somewhat chronically ill. His temperature was 99.2° F. His pulse was 88 and his blood pressure was 132/72 mm. of Hg. Examination of the ears, nose and throat was negative. A funduscopic examination was not remarkable. Slight scleral icterus was noted. The lungs were clear. No abnormalities were found on cardiac examination. Bilateral epitrochlear nodes were palpable. The remainder of the physical examination was negative except for the skin. Numerous red-brown nodules were noted over the face, back, chest and extremities. These varied between 1 and 3 cm. in diameter, and some showed evidence of weeping and ulceration (figures 1, 2, 3).

Laboratory work revealed a hemoglobin of 15.4 gm. and a red blood cell count of 4,000,000. Many white cell counts ranged between 5,000 and 5,850 with 45 to 60% neutrophils and 30 to 40% lymphocytes. A few monocytoid cells were noted. The differential was considered to be entirely normal. A bone marrow study on admission revealed the following:

Myeloblasts	0.5%	Lymphocytes	9.0%
Progranulocytes	0.5%	Monocytes	5.5%
Myelocytes		Plasmacytes	0.5%
Neutrophils	1.5%	Megakaryocytes	0.0%
Eosinophils		Reticulum cells	34.0%
Basophils		Rubriblasts (megaloblasts)	0.5%
Metamyelocytes		Prorubricytes (basophilic normoblasts)	8.0%
Neutrophils	6.0%	Rubricytes (normoblasts)	10.0%
Eosinophils		Melarubricytes	
Basophils		(late normoblasts)	7.0%
Segmented cells			
Neutrophils	12.5%		
Eosinophils	6.0%		
Basophils			

A skin biopsy revealed a lymphoma-type infiltrate consistent with a diagnosis of reticulum cell sarcoma. It was the opinion of the pathology department that this patient had multiple cutaneous areas of reticulum cell sarcoma. During this admission other laboratory work, which proved to be negative or within normal limits, included blood electrolytes, a total protein and albumin-to-globulin ratio, a thymol turbidity, alkaline phosphatase and a urinalysis. A bromsulfalein test on admission revealed 16% dye retention in 45 minutes. A serum bilirubin was 2.2 mg.%, with 0.9 mg.% direct bilirubin and 1.3 mg.% indirect bilirubin. A repeat serum bilirubin done later in the patient's hospital stay was 3.3 mg.%. A blood urea nitrogen was 2[illegible] mg.%. Two chest x-rays were negative. An intravenous pyelogram was not entirely satisfactory but showed no gross abnormalities. A gastrointestinal series revealed some increase in the retrogastric space, and the possibility of a retroperitoneal mass was suggested. The elevated serum bilirubin was felt to reflect direct invasion of the liver with reticulum cell sarcoma.

Because of the history of transitory benefits from spray radiation therapy, it was elected to begin this patient on a course of steroid medication. On July 17 he was started on prednisone, 50 mg. each day in divided doses, with the usual precaution of a low salt and relatively high potassium diet.

Within five days a remarkable regression of the skin nodules was noted, and in the next few days all of the elevated nodules faded, leaving only areas of brown pigmentation (figures 4, 5, 6). In the following weeks these areas of pigmentation continued to fade but did not entirely disappear. On August 8, approximately three

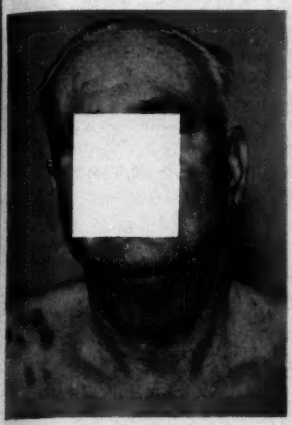

FIG. 4.

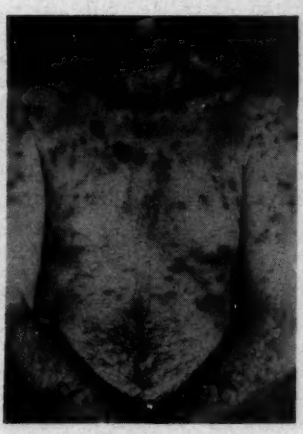

FIG. 5.

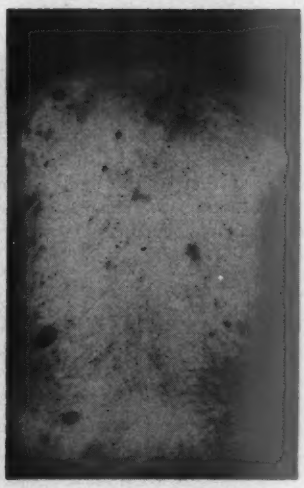

FIG. 6.

Skin manifestations in reticulum cell sarcoma five days after beginning prednisone therapy.

weeks after the beginning of therapy, a biopsy was performed on an area of pigmentation on the anterior chest. Careful examination of sections revealed no evidence of reticulum cell sarcoma. A repeat bone marrow study performed on August 13, almost one month after the start of therapy, showed no evidence of the previously noted reticulum cells and was not considered to be diagnostically abnormal.

The patient continued to feel well but developed some fullness in the face and weight loss, particularly in the lower extremities. After an initial loss his weight stabilized at approximately 182 pounds. His prednisone was gradually lowered to a dose of 15 mg. each day, with no evidence of recurrence of his skin lesions. He was discharged to his home on September 4, 1956, feeling well and greatly benefited. He was followed as an out-patient.

The patient did fairly well after discharge but noticed some weakness. About 10 days after leaving the hospital he noticed a brown nodule in his scalp, and in the next few days similar nodules erupted on the scalp, face and chest. He was readmitted to the hospital on September 20, 1956, appearing extremely ill, with many dark skin nodules over the trunk and head. No scleral icterus was noted on admission. Moist râles were heard at both lung bases. The liver was felt four fingerbreadths below the right costal margin. A splenic tip could not be definitely felt. Several urinalyses and hemograms, including differential smears, were within normal limits.

The patient's dose of prednisone was raised to 40 mg. each day following admission, but his condition deteriorated and he developed jaundice. His spleen became easily palpable 5 cm. below the left costal margin, and he soon was unable to take oral medication because of nausea and vomiting.

On September 25, 1956, intravenous nitrogen mustard therapy was begun, with no definite improvement. During the course of this treatment the patient developed atrial fibrillations, which responded to intravenous digitalis. On September 28, 1956, he became semicomatose, lapsed into shock, and died the following day without further change.

Pathology Summary: Considerable putrefaction had occurred before permission for autopsy was obtained. Gross findings included yellow discoloration of the skin, mucous membranes and sclera. Over the scalp and trunk there were numerous black-purple papillary lesions, the largest approximately 1 cm. in diameter. Moderate sclerotic changes were noted in the coronary arteries. The lungs showed congestion and edema. The spleen weighed 750 gm., and marked postmortem degeneration was noted. The liver weighed 2,700 gm. and presented moderate yellow-brown degeneration. Other gross findings were not remarkable. Microscopic examination of tissue was considered to be unsatisfactory, due to severe postmortem changes. Lymphogenous or leukemic infiltrates were identified in the liver and bone marrow. The findings were felt to be compatible with the antemortem clinical diagnosis.

Discussion

The reticulum cell sarcoma in all its forms remains a difficult problem, from the viewpoint not only of treatment but also of pathologic classification. Pathologists still disagree on the histogenesis of lymphosarcoma and reticulum sarcoma, and they cannot always differentiate these types from the histopathology alone. This problem has been well discussed elsewhere.[7]

The treatment of reticulum cell sarcoma is not satisfactory. Statistics indicate that malignant lymphomas may be found in localized form in 10% of cases, and surgical removal is the treatment of choice in such cases.[8] Among patients with solitary reticulum cell sarcoma treated with surgical extirpation, 24% have been reported to have survived five years.[9]

Although a dramatic response to radiation with the reticulum cell sarcoma may be achieved initially, the ultimate prognosis is unfavorable. Characteristically, the reticulum cell sarcoma runs a malignant course despite an early remission of symptoms. Jenkinson and his group reported eight cases of reticulum cell sarcoma treated with adequate radiation with an average duration of life from the onset of symptoms of two years. Much longer survivals with radiation therapy have been reported.[5]

In the specific treatment of cutaneous reticulum cell sarcoma, two unusual cases reported by Feldaker and his group in 1954 displayed remarkable remissions with the use of repeated doses of intravenous nitrogen mustard.[4]

Steroid therapy has been used primarily in a supportive role in the treatment of the lymphoblastoma. Temporary benefits have been noted.

It was felt that this rather unusual case presented a striking remission with steroid therapy. It is of some note that the skin lesions and bone marrow abnormalities disappeared after the initiation of therapy. The temporary nature of these beneficial effects can be well seen by the patient's late rapid inexorable downhill course.

Acknowledgment

The author wishes to express his appreciation to Lieutenant W. C. Herrick, MC, USN, Lieutenant M. E. McHenry, MC, USN, and other members of the pathology department of the U. S. Naval Hospital, San Diego, California, who contributed considerable time and effort to the pathologic material available in this case and established the correct diagnosis.

Summario in Interlingua

Lymphoblastoma cutanee es le termino usualmente applicate al manifestationes cutanee del lymphomas e del leucemias. Le majoritate de iste manifestationes

es non-specific in natura e variate in forma. Specific lesiones cutanee ab le invasion directe del pelle es minus frequente, specialmente in casos de sarcoma de cellulas reticular. Remissiones ha occurrite in le tractamento de omne formas de sarcoma de cellulas reticular como effecto del uso de mustarda de nitrogeno e de radiation a radios X. Tamen, le morbo recurre, sin reguardo a qual tractamento es usate.

Le presente caso de sarcoma de cellulas reticular manifestava multiple nodulos cutanee de lymphoma invasive. Le patiente esseva tractate con prednisona in doses de 50 mg per die e monstrava un regression dramatic de omne su nodulos cutanee. Areas residue de pigmentation brun esseva negative in studios bioptic, e le medulla ossee del patiente redeveniva normal. Le remission durava circa 10 septimanas. Alora le patiente succumbeva a un recurrentia acute de su morbo le qual se monstrava refractori a omne formas de tractamento. Le necropsia revelava infiltratos lymphomatose in le hepate e le medulla ossee.

Iste caso de sarcoma de cellulas reticular esseva satis inusual, specialmente in vista del breve sed frappante remission effectuate in illo per medio de un therapia a steroide.

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CONGENITAL SERUM PROTHROMBIN CONVERSION ACCELERATOR (SPCA) DEFICIENCY *

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Introduction

It became apparent a decade ago that the conversion of prothrombin to thrombin does not occur solely with the aid of thromboplastin and calcium.

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Ware and his colleagues [1-4] separated a protein fraction from bovine serum, serum AC-globulin, which they thought resulted from the interaction of thrombin with a relatively inert precursor, plasma AC-globulin. This increased the velocity and amount of thrombin formation in an isolated system containing prothrombin, thromboplastin and calcium. Owren [5] found a similar substance evolving during the coagulation process and called it factor VI. Alexander et al.[6-9] reported on a prothrombin conversion accelerator in serum, SPCA. Milstone[10] also observed the transformation of a plasma globulin, prothrombokinase, during the first phase of coagulation, into thrombokinase, an active enzyme, which also accelerates prothrombin conversion.

Many terms have been employed in describing plasma AC-globulin and serum prothrombin conversion accelerator. To avoid confusion Owen and his associates [11] suggested a simplified nomenclature where the terms "labile factor (L. F.)" and "stable factor (S. F.)" are employed and define resistance to storage. Labile factor is used for Owren's factor V, or proaccelerin (the precursor of accelerin or factor VI), plasma AC-globulin (Seegers), or prothrombin accelerator (Fantl). Stable factor is synonymous with the more recently discovered accelerator, SPCA (Alexander [12]), factor VII (Koller [13]) co-thromboplastin (Mann [14]) or convertin (Owren [15]), the plasma precursor of which is called proconvertin.

Plasma AC-globulin is labile and not readily adsorbed by $BaSO_4$ or $BaCO_3$, while SPCA is a relatively stable serum factor which is adsorbed by these substances. The latter factor arises from a plasma precursor which, along with prothrombin, is adsorbed by $BaSO_4$ and elutable by citrate. Both plasma AC-globulin and SPCA and its precursor are adsorbed by $Mg(OH)_2$. The conversion of prothrombin to thrombin during normal coagulation proceeds with ever-increasing velocity until the very moment of clotting, or immediately afterwards, when thrombin formation becomes explosive. Plasma AC-globulin speeds up the pace early in prothrombin conversion, but the reaction is further markedly accelerated as SPCA is evolved during clotting. Although AC-globulin is consumed during coagulation while SPCA is being elaborated, AC-globulin is not its precursor.

Since Alexander and his associates [8] reported the first case of hemorrhage due to congenital SPCA deficiency, only a very few others [16-28] have appeared in the literature. It is the purpose of this report, therefore, to present a case of congenital SPCA deficiency and discuss its salient diagnostic features.

Case Report

A 65 year old white female was admitted to Bellevue Hospital for the tenth time on February 15, 1956, with epistaxis of one week's duration. She had had recurrent epistaxes since early childhood. Though the exact age of onset could not be recalled, she knew definitely that they had begun before 10 years of age. She could not remember the degree of menstrual bleeding, but did state that each of several pregnancies was terminated by a miscarriage. A hysterectomy was performed in 1924 following a period of severe uterine bleeding. One of her nine sisters died of a uterine hemorrhage at 18 years of age.

The patient had been a janitress in a saloon during the last 10 years, and admitted to consuming five ounces of whiskey daily.

Her first admission to Bellevue Hospital was in 1931, with hematuria of undetermined origin. Epistaxes brought her to the clinic several times during 1937. Hemoptysis of unknown etiology occurred in 1941, and epistaxis hospitalized her in 1946.

Recurrent epigastric pains caused the patient to visit the clinic in 1941 and subsequently. Physical and laboratory examinations were negative until 1947, when an epigastric mass was found. Laparotomy was performed in September, 1947, at which time the liver was found to have a large quadrate lobe, and there was a lipoma in the falciform ligament. It was thought that the palpated mass in the epigastrium had consisted of the enlarged quadrate lobe and the lipoma. Plasma transfusions were given, and the patient had an uneventful postoperative course.

Seven weeks after laparotomy she became jaundiced and was re-admitted with the diagnosis of homologous serum hepatitis. Repeated epistaxes occurred during this three-month hospitalization. Several blood transfusions were given in addition to vitamins C, K, B complex, rutin and liver extract. Prothrombin times were 17 seconds (control, 11), 21 seconds (control, 13), and 16 seconds (control, 12). Examination of the sternal bone marrow revealed normoblastic hyperplasia. The Rumpel-Leede test was negative. At discharge the icterus index was 12; cholesterol/cholesterol esters was 280/167 mg.%; albumin, 4.6, and globulin, 3.3 gm.%; cephalin flocculation test, negative; alkaline phosphatase, 2.7 Bodansky units.

The patient was re-admitted to the hospital in March, 1948, complaining of hematuria and right flank pain of four weeks' duration. There was evidence of advanced renal failure in addition to severe anemia and prolonged prothrombin times (24 to 64% of normal activity). There were repeated episodes of flank pain and hematuria. The patient received a total of 3,400 c.c. of whole blood in 11 transfusions. The final diagnosis was chronic diffuse glomerulonephritis.

She was next admitted in November, 1948, complaining of weakness, headaches, anorexia and right upper quadrant abdominal pains. Tests again demonstrated damage in all areas of renal function. Bone marrow examination revealed normoblastic hyperplasia. The final diagnosis again was chronic diffuse glomerulonephritis.

The patient came to the clinic for varying complaints from December, 1948, to February, 1954, when she was admitted to Bellevue for the seventh time. She complained of epigastric pain, weakness, dizziness and exertional dyspnea. The spleen tip and liver edge were palpated. The leukocyte count was 2,850 per cubic millimeter, with 15 transitional and 45 mature neutrophils, 30 lymphocytes, 6 monocytes and 4 eosinophils per 100 white blood cells. The platelet count was 230,000 per cubic millimeter. The final impression was leukopenia secondary to splenic disease.

In October, 1954, the patient was admitted to the hospital for the purpose of varicose vein surgery. The latter was not performed because of her bleeding tendency.

The ninth hospital admission was in March, 1955. The patient told of black stools, abdominal pains, and episodes of fainting during the previous two weeks. On admission the stools were brown and remained negative to guaiac test. Hemoglobin was 8.5 gm.%. X-ray study of the upper gastrointestinal tract was negative. The gall-bladder was poorly visualized with contrast material. An oral starch tolerance test was normal. Serum amylase level was 86 Somogyi units. During this admission SPCA deficiency was diagnosed. The studies leading to this diagnosis are summarized later.

Physical examination on the tenth admission found the patient to be a well developed, moderately obese white female in shock, with a systolic blood pressure of 70 mm. Hg. She was placed in shock position and the blood pressure rose rapidly to 120/65 and later to 150/80 mm. Hg. Temperature was 101° F. rectally. There were gross tremors of the hands at rest. The skin was cool and moist, with several

diffusely scattered seborrheic keratoses. The ocular fundi had grade I changes. A bloody nasal packing was in the right nostril, and fresh blood was seen in the pharynx. The trachea was deviated to the right, and there was a dorsal scoliosis with convexity to the right. The lungs were clear to percussion and auscultation. The cardiac apical impulse was not felt, and the left border of cardiac dullness was 2 cm. outside of the midclavicular line in the fifth left intercostal space. The ventricular rate was entirely irregular at 100 per minute. A short systolic murmur was heard at the base. The liver edge was 2 cm. below the costal margin in the right midclavicular line and was tender. The spleen was percussed down to the left costal margin. Varicose veins were present in the legs. The pedal pulses were weak.

The urine had a specific gravity of 1.015. It contained 20 mg.% protein, no sugar or acetone, several hyaline, waxy and granular casts per low power field, and 4 to 5 white blood cells and 2 to 3 red blood cells per high power field. Urine bile test was 2 plus positive, and urobilinogen was positive in a 1:20 dilution. The red blood cell count was 3,980,000 per cubic millimeter; hemoglobin, 9 gm.%; hematocrit, 30%. The leukocyte count was 4,250 per cubic millimeter, with 13 transitional and 64 mature neutrophils, 14 lymphocytes and 9 monocytes per 100 white blood cells. Target cells and pencil forms were seen on blood smears. Plasma prothrombin time was 25 seconds (control, 13), and serum prothrombin time was 54 seconds (normal, over 30 seconds). Platelet count was 54,000 per cubic millimeter; bleeding time, 1½ minutes; clotting time (Lee-White), 10 minutes. There was a 3 plus clot retraction. Reticulocyte count was 4.6%. Coombs' test, direct and indirect, was negative. Fecal urobilinogen was 44 Ehrlich units per 100 gm. (normal range, 75 to 333). Erythrocyte sedimentation rate was 21 (Wintrobe, corrected). Blood type was AB, Rh positive. Blood urea nitrogen was 15 mg.%; plasma creatinine, 1.75 mg.%. Cholesterol was 202; cholesterol esters, 121 mg.%; icteric index, 9; total bilirubin, 2.0, and prompt, 0.6 mg.%; cephalin flocculation, negative; albumin, 5.0, globulin, 2.5 gm.%; alkaline phosphatase, 4.0 Bodansky units; 19% retention of bromisulfalein after 45 minutes. Mazzini test was negative. Chest x-ray revealed calcification in the aortic knob as well as in the right hilar glands; transverse diameter of the heart within normal limits, and scoliosis of the dorsal spine with resultant thoracic asymmetry. Radiographs of the abdomen showed suggestive evidence of splenic enlargement, calcification of the abdominal aorta as well as of the splenic artery, and a somewhat small left kidney. Electrocardiogram revealed atrial fibrillation, incomplete right bundle branch block, and diphasic T-waves in the left ventricular type leads.

The nasal bleeding was controlled within two days by anterior and posterior packings, and was followed on the second day by 500 c.c. of whole blood. The hemoglobin rose from 9.5 to 11.0 gm.%. The plasma prothrombin time remained elevated during the three weeks of hospitalization, apparently unaffected by intramuscular vitamin K and intravenous vitamin K_1 oxide. The platelet count rose to 160,000 per cubic millimeter. Two weeks after admission regular sinus rhythm returned and the electrocardiogram was within normal limits. No bile was found in the urine at the time of discharge from the hospital.

The patient has been seen several times in the clinic since discharge and has been receiving oral iron therapy. Her hemoglobin has remained at 10.5 to 11.5 gm.%. In October, 1956, the plasma prothrombin time was 37 seconds and was corrected to 17 seconds by normal serum.

Discussion

The first prothrombin times (Quick one-stage) determined in this case were performed during and immediately after the episode of homologous serum hepatitis in late 1947. They ranged from 21 (control, 13) to 17 (control, 11)

seconds during the active hepatitis and were 16 (control, 12) seconds during convalescence. Subsequent determinations during November and December, 1948, ranged from 20 (control, 13) to 17 (control, 13) seconds; during February and March, 1954, it was 20 (control, 12) seconds; and in October, 1954, 46 (control, 12) seconds. Until 1955, when SPCA deficiency was demonstrated, it was erroneously thought that the prolonged prothrombin times were due to hypoprothrombinemia.

In March and April, 1955, complete coagulation studies were performed, at which time the Lee-White clotting time was 12 minutes (normal, 12 to 18); bleeding time, 1.5 minutes; platelet count, 173,500 per cubic millimeter; clot retraction, 4 plus. Table 1 demonstrates that the patient had a prolonged plasma prothrombin time and a normal serum prothrombin time (over 30 seconds). The plasma prothrombin time was corrected by normal plasma, stored plasma

TABLE 1

Basis for Diagnosis of SPCA Deficiency

Patient's Plasma	Patient's Serum	Normal Plasma	Normal Serum	$BaSO_4$ Normal Plasma	$BaSO_4$ Normal Serum	Stored Normal Plasma	Prothrombin Time Seconds
100*							43.8
	100						73.4
90		10					19.9
90				10			43.0
50		50					15.7
						100	33.4
90						10	19.9
10						90	18.3
90			10				15.1
90					10		39.1
	90		10				45.1

* These numbers represent the relative proportions of the specified substances in per cent.

and normal serum; it was not corrected by barium-sulfated normal plasma or barium-sulfated normal serum. Thus, treating plasma or serum with barium sulfate removed the factor which corrected the patient's prothrombin time. This factor was not destroyed by storing plasma, or by allowing blood to clot. Since the patient's plasma corrected the prothrombin time of stored plasma, it can be concluded that the patient's plasma contained the relatively labile factor, AC-globulin, and that the factor which was missing from the patient's plasma is stable during the storage of normal plasma. The missing factor, therefore, was SPCA.

The patient's serum did not shorten to a significant degree the prothrombin time of normal serum, which would have happened if the patient's serum contained prothrombin. Since the patient's plasma contained normal amounts of prothrombin, it can be assumed that the prothrombin was consumed during clotting, i.e., a normal prothrombin consumption. This consumption indicates the presence of thromboplastic factors in normal amounts. In March, 1956, these factors were demonstrated definitely to be present by a normal thromboplastin generation test.

TABLE 2

Effect of Transfusion of Normal Blood on Patient's Prothrombin Time

	Patient's Plasma Prothrombin Time Seconds
Prior to transfusion	39.6
During transfusion—after 100 c.c.	28.6
after 200 c.c.	24.4
after 300 c.c.	24.7
after 400 c.c.	23.1
after 500 c.c.	22.6
Following transfusion— 2 Hrs.	25.0
4	29.4
6	31.4
8	31.6
12	36.9
16	37.4

(Prothrombin time of bank blood used for transfusion, 16.4 seconds.)

The patient's thrombin clotting time was normal, indicating the presence of adequate amounts of fibrinogen, and no fibrinolysin could be found in the blood.

Transfusion studies (table 2) indicated that the patient's prothrombin time was only partially and temporarily corrected by whole blood. The prothrombin time began to rise two hours after the transfusion was ended, and reached pre-transfusion levels within 12 to 16 hours after the transfusion was completed. Plasma drawn from the patient immediately after the transfusion was ended was able to correct the prolonged prothrombin time of her own plasma which had been drawn just before the transfusion was started. In view of the aforementioned studies, it is apparent that the transfused blood supplied the patient's missing factor, SPCA. Why the therapeutic effect of so-called "stable" factor is so short-lived is not so readily apparent.

Anti-SPCA was ruled out by incubating normal plasma with the patient's plasma. It was found that the factor in normal plasma which corrects the patient's plasma prothrombin time is not destroyed by exposure to the patient's plasma (table 3).

Since Alexander and Goldstein [29] reported probable cases of SPCA deficiency in patients with acquired hepatic disease, one could suggest that this patient, too,

TABLE 3

Incubation of Patient's Plasma with Normal Plasma

	Patient's Plasma	Normal Plasma	Prothrombin Time Seconds
A.	50*	50	12.6
		100	12.0
B.	50	50	13.7
		100	13.5

A. Prothrombin time determined immediately.

B. Prothrombin time determined after incubation for several hours.

* These numbers represent the relative proportions of the specified substances in per cent.

might belong to that group. However, the history of onset of the bleeding episodes in early childhood and the paucity of significantly positive liver chemistries make this unlikely. The accompanying hypoprothrombinemia that one would also expect to find in hemorrhagic diathesis due to hepatic insufficiency is also not present.

Summary

1. A case of congenital serum prothrombin conversion accelerator (SPCA) deficiency is presented.

2. The methods employed in diagnosing the condition are discussed.

Summario in Interlingua

Es presentate le caso de un femina de racia blanc de 65 annos de etate con un historia de episodios de sanguination ab varie sitos depost le tempore de su infantia. In 1955, carentia del accelerator del conversion de protrombina del sero (ACPS) esseva demonstrate in iste patiente. Previemente su prolongate tempores prothrombinic habeva essite interpretate erroneemente como le effecto de hypoprothrombinemia.

ACPS resulta ab un precursor in le plasma e es un relativemente stabile factor seral. Insimul con prothrombina illo es adsorbite per $BaSO_4$ e pote esser eluite per medio de citrato. Isto contrasta con le comportamento de ac-globulina del plasma, le qual es labile e non facilemente adsorbite per $BaSO_4$.

Studios del coagulation revelava un normal tempore de sanguination e un normal tempore coagulatori de Lee-White como etiam un normal numeration de plachettas e un retraction del coagulo de 4 plus. Ben que le patiente habeva un prolongate tempore prothrombinic del plasma, le tempore prothrombinic del sero esseva normal (i.e. plus que 30 secundas). Le tempore prothrombinic del plasma esseva corrigible per plasma normal, per plasma immagasinate, e per sero normal. Illo non poteva esser corrigite per plasma o sero normal que habeva essite tractate con sulfato de barium. Ergo, tractar plasma o sero con sulfato de barium eliminava le factor que corrigeva le tempore prothrombinic del patiente. Iste factor non esseva destruite per immagasinar le plasma o per permitter le coagulation de sanguine. Viste que le plasma del patiente corrigeva le tempore prothrombinic de plasma immagasinate, le conclusion se imponeva que le plasma del patiente contineva le relativemente labile factor ac-globulina e que le factor absente ab le plasma del patiente es stabile durante le immagasinage de plasma normal. Ergo, le factor absente esseva ACPS.

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SARCOIDOSIS WITH INVOLVEMENT OF THE PITUITARY GLAND*

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Sarcoidosis is a fairly common disease. However, pituitary involvement by sarcoidosis is exceedingly rare. We have observed a patient with proved sarcoidosis with probable involvement of the pituitary gland.

Case Report

A 32 year old white male machinist was first admitted to this hospital in 1945 because of small lumps in the pretibial area which were diagnosed as erythema nodosum. The x-ray of the chest showed a distinct hilar lymphadenopathy. No glands were palpable, and there was no testicular atrophy. Sputa were negative for fungi and tuberculosis.

The patient's next admission was in 1951 because of fatigue and cough. The liver was 5 cm. below the costal margin, and the spleen was palpable. There was dryness of the skin, and the hair was thin. Palpable lymph nodes were present. X-ray of the chest showed linear infiltrations extending from the hili to both bases. X-rays of the hands were normal. Total protein was 6.3 gm.%; albumin, 3.4; globulin, 2.9; A/G ratio, 1.2; serum calcium, 10 mg./100 c.c. Alkaline phosphatase was 5.4 Bodansky units. Thymol turbidity was 6 units. Biopsy of the lymph nodes was obtained and the slides were typical of Boeck's sarcoid. The patient improved on treatment with cortisone. A second lymph node biopsy, performed on February 15, 1952, was still typical of sarcoidosis but showed less involvement. This part of the patient's history has been published elsewhere in greater detail, including photomicrographs of the lymph nodes showing typical sarcoidosis.[1]

He was admitted again in January, 1953, because of a "cold." Hepatosplenomegaly and nuchal lymphadenopathy were present. The total protein was 6.9 gm.%; albumin, 3.4; globulin, 3.5; A/G ratio, 0.97. Thymol turbidity was 6 units. The skin test was negative for tuberculosis. The patient responded again to cortisone treatment, 25 mg. daily, which he continued to take for almost three years, and felt well until the summer of 1956, when he began to drink approximately three gallons of water per day. He also urinated frequently and had nocturia three to five times. His strength had remained about the same. Libido was decreased. No shortness of breath or ankle edema was present. There had been no infections during the winter. There were no enlarged lymph nodes. He had had no headaches.

Physical Examination: Temperature, 97° F.; pulse, 80; respirations, 20; blood pressure, 134/84 mm. Hg. The patient was a well developed, obese young white male in no acute distress. His skin was thick and dry. There was a sparsity of hair on the chest and a lack of hair in the axillae. The breasts were enlarged. There was no pigmentation of the skin or gums. The lungs were clear to percussion and auscultation. Cardiac examination was negative. The liver was palpable 3 cm. below the right costal margin, the spleen 3 cm. below the left costal margin. Lymph nodes were not palpable, and there were no erythematous nodules. Eye examination showed normal discs, normal eye grounds and normal visual fields.

Urinalysis: reaction, acid; specific gravity, 1.004 (repeated random specimens

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varied from 1.004 to 1.005); sugar, negative; albumin, negative; microscopic, negative. His daily urine output was from 6,000 to 8,000 c.c. Urinary concentration test was performed with extreme difficulty. During the 12-hour test his total urinary output was 400 c.c., and the highest concentration was 1.021. The patient suffered very much during this test. He became weak and apprehensive, perspired, had tremors, and stated that he would never again go through a similar ordeal.

Blood serologic test for syphilis was negative. White blood count, 6,300; hemoglobin, 14.8 gm.%; hematocrit, 45%; sedimentation rate, 30 mm./hour. Circulating eosinophil count was 78/cu. mm., and a repeat circulating eosinophil count was 112/cu. mm. A Thorn test with ACTH on March 8, 1956, showed initially 88/cu. mm., and four hours after ACTH showed 56/cu. mm. A Thorn test with adrenalin on March 9, 1956, was 88/cu. mm., and 44/cu. mm., respectively. Nonprotein nitrogen, 35 mg.%; fasting blood sugar, 86 mg.%. CO_2, 23.3; sodium, 140; potassium, 5.3; chlorides, 107.7 mEq./L. Total protein, 6.7 gm.%; albumin, 4.4; globulin, 2.3; A/G ratio, 1.9. Bromsulfalein, 4% retention in 45 minutes. Cholesterol, 275 mg.%; cholesterol esters, 69%. Serum bilirubin, 0.4 mg.%; van den Bergh: direct, 0.0; indirect, 0.4; thymol turbidity, 5 units; prothrombin time, 42%. Serum calcium, 5.7 mEq./L.; inorganic phosphorus, 3.8 mEq./L.; acid phosphatase, 1.9 King units; alkaline phosphatase, 3.8 Bodansky units. Basal metabolic rate, minus 31%. Tuberculin test, first and second strength, negative. Sulkowitch test, negative. C reactive protein, negative. Power-Kepler test formula A was 15 on March 14, 1956; 14 on May 15, 1956; and 40 on August 13, 1956, after treatment with cortisone. Glucose tolerance test: fasting, 105 mg.%; one-half hour, 121; one hour, 120; two hours, 115; three hours, 105; four hours, 105. Intravenous insulin test: fasting, 60 mg.%; 20 minutes later, 45; 30 minutes later, 40; 45 minutes later, 27; 60 minutes later, 75; 90 minutes later, 85; 120 minutes later, 86 mg./cu. mm. Follicle-stimulating hormone, less than 6.6 mouse units per 24 hours. X-ray of the chest was negative. Spinal fluid examination was normal (initial pressure, 180 mm. H_2O; final pressure, 90; fluid, clear; cell count: two lymphocytes; total proteins, 24; serologic test for syphilis, negative). Scout film of the abdomen showed minimal hepatosplenomegaly. X-ray of the skull on two separate occasions showed the sella turcica to be within normal limits. X-rays of the hands and feet were negative. Electrocardiogram was within normal limits. Electro-encephalogram was normal.

Protein-bound iodine test was 5.8 μg. per 100 c.c. I^{131} uptake was 8% on one occasion and 16% on another. Twenty-four hours after the patient received 10 units of thyroid-stimulating hormone ("Thytropar," Armour & Company), the I^{131} was 38% and the protein-bound iodine was 29.6 μg.%. The 11-oxysteroid test was 5.4 mg./24 hours. The 17-ketosteroid test showed a total of 92.5 mg./24 hour specimen, and a second 17-ketosteroid test was 46.2/24 hour specimen. The Hickey-Hare test (loading with intravenous saline to differentiate between diabetes insipidus and psychogenic water drinking) was positive for diabetes insipidus.

Electrophoretic studies of the serum protein showed normal distribution. Biopsy of the testicle showed atrophy. Liver biopsy showed moderate fatty metamorphosis.

The patient was given Pitressin Tannate intramuscularly. He responded immediately and had to drink less water (2,000 to 3,000 c.c.), and a random specimen of the urine showed a specific gravity of 1.026. He was then put on Pitressin by intranasal insufflation. For financial reasons the patient could not be regulated on thyroid-stimulating hormone, and was given thyroid extract instead. He was also given testosterone, 25 mg. twice weekly, and cortisone, 12.5 mg. twice a day.

Discussion

Only a few cases of diabetes insipidus due to sarcoidosis with postmortem proof have been reported.[2-6] Some cases had clinical manifestations of diabetes

insipidus and of genital dystrophy, and postmortem examination in those cases showed involvement of the posterior and partial involvement of the anterior part of the pituitary gland.[2, 6] In a few cases (without autopsy) a clinical diagnosis of sarcoidosis was made and the associated diabetes insipidus was explained as due to an involvement of the pituitary gland by sarcoidosis.[7]

The high specific gravity which the concentration test showed is not, in our opinion, against the diagnosis of diabetes insipidus, but requires some explanation. Dann,[8] in reporting a case of diabetes insipidus with a random specific gravity of 1.014, stated that he does not believe that "an occasional elevation mitigates too strongly against the diagnosis." It should be noted that, in our case, random urine specimens showed a specific gravity of 1.004 and 1.005, and only on a controlled urinary concentration test was this high specific gravity obtained. However, the patient developed tremors, weakness and apprehension, and suffered very much during the procedure. The unquenchable thirst, the polyuria, the low specific gravity of the urine, the immediate dramatic changes after Pitressin, and the fact that he again had polydipsia and polyuria when he occasionally discontinued Pitressin, are strongly in favor of diabetes insipidus. Finally, psychogenic polydipsia ruled out on the basis of the positive Hickey-Hare test, in addition to the Pitressin response. Evidently there are in diabetes insipidus, as in any other disease, degrees of severity.

The patient also had anterior pituitary gland involvement. The thin hair, the thick skin, the low basal metabolic rate, the low I^{131} uptake and the low-normal protein-bound iodine before stimulation with thyroid stimulating hormone, and the high values of I^{131} uptake and protein-bound iodine after stimulation with thyroid-stimulating hormone, prove that the thyroid gland was not involved primarily, but that we are dealing with a secondary (pituitary) myxedema.

The gonadal involvement is manifested by the small testicles, the diminished libido, and the testicular biopsy which showed atrophy.

The patient does not have Simmonds' disease. The adrenals were still capable of functioning and tried to compensate for the testicular atrophy with a high 17-ketosteroid output. It is known that, in male animals, castration is followed by adrenal cortical hypertrophy.[9]

Any lesion involving the supra-optic nuclei or the hypothalamus or the supra-pituitary stalk might result in diabetes insipidus. Conditions like infections, metastatic tumors, embolism, postpartum necrosis, syphilis, tuberculosis, leukemia and lymphogranulomatosis have to be ruled out. The abovementioned conditions can by history and by physical findings easily be ruled out.

We do not think that cortisone was responsible for the pituitary gland involvement in this case. It is true that continuous administration of high doses of cortisone depresses the ACTH output by the anterior pituitary gland and thereby might cause it to atrophy. The small dose of 25 mg. of cortisone daily does not cause such changes. Our patient at no time showed cushingoid signs. Even in cases where great amounts of cortisone were given, with definite development of cushingoid signs, and where the postmortem examination showed marked atrophy of the adrenal cortex, the anterior lobe of the pituitary showed normal morphology.[10] Neither can cortisone in any way be incriminated for the posterior gland involvement, because "no evidence of a direct action of cortisone on the posterior pituitary gland or on the release of its hormones has been reported."[11]

Evidently only certain parts of the anterior pituitary were involved at this stage of the disease. The severity of diabetes insipidus depends on the degree of involvement of the anterior pituitary because, if the anterior pituitary is not functioning at all, it cannot stimulate the posterior pituitary and the diabetes insipidus ceases.[12, 13] It is possible that the relatively moderate form of diabetes insipidus in our case might be explained by partial involvement of the anterior pituitary.

Since this patient has a histologically proved sarcoidosis, it is logical to assume that the involvement of the pituitary gland is caused by sarcoidosis.

Cases of involvement of the pituitary by sarcoidosis with clinical manifestations of diabetes insipidus and genital atrophy have been reported,[2, 6] but to our knowledge no case involving the pituitary has been reported that showed clinical manifestations of pituitary myxedema, diabetes insipidus and genital atrophy.

The fact that cortisone, which the patient has been taking over a prolonged period of time, caused some improvement (the hilar lymphadenopathy present on the first admission disappeared on cortisone treatment and was not present on his later admissions), but did not prevent the eventual involvement of the pituitary gland, is of interest.

Summary

A case is reported of proved sarcoidosis with diabetes insipidus, pituitary myxedema and testicular atrophy, presumably due to sarcoid infiltration of the posterior and of portions of the anterior part of the pituitary gland. The rarity of the involvement of the pituitary gland by sarcoidosis is stressed. Cortisone treatment did not prevent this complication.

Summario in Interlingua

Es reportate un caso de sarcoidosis con affection del glandula pituitari, occurrente in un masculo de racia blanc—machinista de profession—de 32 annos de etate.

In 1945 le patiente disveloppava erythema nodose. In 1951 ille esseva examinate a causa de fatiga e tusse, e le presentia de hepatosplenomegalia e de palpabile nodos lymphatic esseva constatate. Le examine roentgenographic del thorace monstrava lymphadenopathia. Le biopsia de nodos lymphatic esseva typic de sarcoide de Boeck. Le patiente esseva tractate con cortisona. Ille se meliorava.

In 1953 le patiente esseva re-examinate a causa de un catarrho. De novo ille monstrava hepatosplenomegalia e lymphadenopathia nuchal. Ille respondeva a cortisona e continuava prender lo durante quasi tres annos. Ille se sentiva ben.

In 1956 ille esseva re-admittite a causa de un sete insatiabile que le fortiava a biber circa 12 litros de aqua per die.

Le examine physic monstrava un pelle sic e spisse, sparsitate de capillos, gynecomastia, hepatosplenomegalia, e le absentia de palpabile nodos lymphatic. Specimens de urina, prendite al hasardo, revelava un basse gravitate specific. Thorace, cranio, e manos esseva roentgenographicamente normal. Le examine del fluido spinal esseva normal. Etiam le electrocardiagramma e le electro-encephalogramma esseva normal. Le fundo ocular e le campos de vision esseva normal. Le acceptation de I^{131} e le nivello de iodo ligate a proteina esseva basse, sed post le administration de hormon thyroido-stimulatori, ambe ille valores se monstrave elevate. Isto indicava que le myxedema esseva de origine pituitari. Le test de Hickey-Hare esseva positive pro diabete insipide. Un biopsia testicular monstrava atrophia. Le patiente esseva tractate con pitressina, con un responsa immediate e dramatic.

Esseva concludite que le patiente habeva un affection del glandula pituitari posterior, manifeste per le diabete insipide, e un affection partial del pituitario anterior, manifeste per le myxedema pituitari e le hypogonadismo.

Reportos de diabete insipide causate per sarcoidosis es rar. Secundo nostre informationes, nulle caso se trova in le litteratura in que le glandula pituitari es afficite, con manifestationes clinic de diabete insipide, myxedema pituitari, e atrophia genital.

Es discutite le diagnose differential del conditiones que causa affectiones del glandula pituitari. Es etiam signalate que le administration de cortisona, que effectuava un melioration al comenciamento del morbo, non preveniva le disveloppamento ulterior de un affection del glandula pituitari.

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EDITORIAL

MEDICINE'S GENETIC HORIZONS *

For something over 500,000 years there have existed on this earth species of man with a cranial capacity approaching that of modern man. For at least 99% of that time span the generation-to-generation rate of cultural change has been, viewed from our current vantage point, almost unbelievably slow. By cultural change I mean nothing more profound than changes in the circumstances of day-to-day living. It took something like 75,000 years for the rough Chellean hand-axe to be replaced by the more even, symmetric Acheulian hand-axe in Western Europe during the Pleistocene. Then, starting with the Agricultural Revolution, and accelerating with the Industrial Revolution, things began to happen. Figure 1 is a very crude attempt to represent graphically this rate of progression. Any such attempt is foredoomed to failure in matters of detail, but concerning the general shape of the curve there can be no mistake.

In the final analysis, much of this change can be summed up in one phrase: man's increasing control over his environment. Nowhere is this increasing control more vividly reflected than in the practice of medicine. Two hundred years ago, perhaps 60 to 80% of the nonsurgical illnesses to which the physician the world over might devote himself were the result either of extrinsic agents of disease, primarily bacteria, viruses, and a variety of parasites; of dietary deficiencies; or of inclement weather. This situation still obtains in many parts of the world. But today in this country, probably less than 20 to 40% of human illness comes under this category. I might say that I have devoted some effort to attempting to document and refine that statement, from a perusal of both old and modern medical texts and old and modern vital statistics, but have been forced to conclude that neither is a very good index to how a physician spends or spent his time, the former emphasizing the unusual and the latter not adequately reflecting the time expended in the management of the case. Be that as it may, an increasing proportion of the physician's time is certainly being devoted to diseases which, in one way or another, are the result of our changing environment and which stem from the inability of the individual to cope with these changes.

The thesis to which I should like to address myself is this: Man, who is without doubt an enormously adaptable organism, is being thrust at a constantly accelerating rate into environmental situations in which he has not previously been tested. It is high time we examined with care the proposition that there may be genetically imposed limits to man's adaptabil-

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ity. Organic evolution provides the mechanism whereby man or any other animal evolves to meet changing conditions. However, there are limits to the rate of evolutionary change. In this highly competitive world of today there is, in my opinion, a real possibility of creating a culture in which, without being given the time in generations for the necessary genetic adjustments, a large fraction—perhaps a majority—of the population cannot function without developing a variety and profusion of maladaptation syndromes. By maladaptation syndromes I refer to such diverse entities as the so-called stress diseases, severe psychoneurosis, or early atherosclerosis and coronary heart disease. That there is to some extent a genetic determinant in these conditions can scarcely be doubted, although the de-

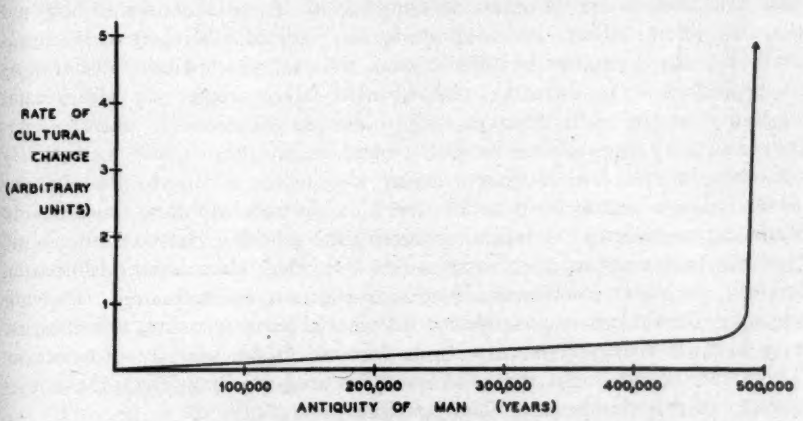

FIG. 1. Diagrammatic representation of the rate of cultural change during the last 500,000 years.

tails remain unknown. While these diseases have to some extent been with man for a long time, and while some fortunate individuals can undoubtedly face an intensification of the Atomic Age Culture both unscathed and unperturbed, in a population sense we can reach a point where the medical and social burdens imposed by these diseases become man's most pressing problem. This problem will be of greatest magnitude where large areas, such as Africa, make the cultural transition relatively rapidly. The apparently greater frequency and severity of hypertension in the American Negro may be an illustration in point.

Furthermore, at the very time when the species stands in urgent need of evolving to meet changing conditions, the medical profession may unknowingly be interfering with these necessary adjustments. This interference may proceed along diverse pathways. There is, on the one hand, the fact that in our efforts to eliminate certain causes of morbidity and mortality we may unwittingly be thwarting the evolutionary mechanism for ridding the human species of the undesirable genes which are constantly

arising through mutation. There is, on the other hand, the possibility that, by our increasing exposure of the human species to ionizing radiation and a variety of new drugs which, like radiation, may be mutagenic, we are feeding mutations into the population at a sufficiently accelerated rate that, with our means of eliminating these mutations already impaired, the inevitable result is an accumulation of these mutations in the germ plasm. Since the majority of mutations have undesirable effects, such an accumulation will be detrimental to the welfare of the human species.

Let us now briefly examine some of the facets of that thesis. First, to what extent has our civilization thwarted those mechanisms of natural selection which brought our species to its present state? Would that we knew! Biologically speaking, an individual's success is measured by the number of descendants he leaves behind. Differences in reproductive performance are brought about either by differential mortality or by differential fertility. In many primitive cultures, infant mortality approaches or even exceeds 500 per 1,000 births. By contrast, in the United States today the figure is more like 30 per 1,000. There seems little doubt that this decline in infant mortality to some extent indicates a lessening of natural selection, but we are in no position to quantitate this impression. On the other hand, differential fertility, the other mechanism of natural selection, is increasing. Depending upon the factors responsible for differential fertility today, this increase may indicate either an increase or a decrease in the severity of selection. There can be no doubt that selective pressures are changing—the consequences of this change have thus far eluded quantitation.

Let us turn now to the question of whether, in addition to thwarting the only means whereby the population rids itself of undesirable mutations, namely, through differential survival and reproduction, we of the medical profession are making a bad situation worse by actually employing procedures that result in increased mutation rates. The agent under most active scrutiny these days is ionizing radiation. There is no time to do more than mention this issue. Elsewhere I have spelled out in some detail my belief that, whereas there can be no doubt of the reality of the problem posed by our increasing exposure to radiation, geneticists are in no position to give this problem more than a very inexact treatment.[1, 2] In addition, it is not commonly realized that many of the drugs in use today have been shown to have mutagenic effects on experimental organisms. The list of such drugs includes ether, chloral hydrate, codeine, benzedrine, cortisone, urethane, colchicine, peroxides, chelating agents, and purine and pyrimidine antagonists. The possible role of these in increasing human mutation rates has

[1] Neel, J. V., and Schull, W. J.: The effect of exposure to the atomic bombs on pregnancy termination in Hiroshima and Nagasaki, National Academy of Science, National Research Council Publication No. 461: xvi and 241, 1956.

[2] Neel, J. V.: The delayed effects of ionizing radiation, J. A. M. A. **166**: 908, 1958.

been touched upon by a number of investigators.[3, 4, 5, 6] The geneticist, in pressing his arguments with both the public and the medical profession, frequently is at a tactical disadvantage because of the aura of unreality which surrounds the effects on subsequent generations in which he deals. To the extent, however, that leukemia reflects the occurrence of somatic mutations, we may have in our own generation very tangible evidence for increasing mutation rates.[7, 8, 9]

Man, after something like 500,000 precarious years on this planet, has now succeeded in grasping firmly the reins of his own destiny. With this development come awesome responsibilities, in which no group shares to a greater extent than does the medical profession, unless it be the nuclear physicist, whose dawning appreciation of what he has done is so forcibly presented in Snow's novel, "The New Men." Who of us has not with pride identified himself with Sir Luke Fildes's wonderful portrait of a physician keeping lonely vigil by the bedside of sick child? The physician's devotion to the individual patient is still unchallenged in a world of rapidly changing values. But, with signs that the human species as a whole may be confronted with medical problems no less serious than those of the child in Fildes's portrait, who in this time of transition is keeping similar vigil over the species? We are all familiar with the complex apparatus of modern medicine, which briskly and efficiently swings into action when a patient with congenital heart disease enters hospital for surgery, or a patient with an acute renal shutdown comes in for dialysis. But, in our concern for the individual, have we forgotten to set up the team which has as its concern the species as a whole?

This is a period of soul searching in medical education. Wood[10] stated the central issue very succinctly when, brushing aside a number of superficial developments, he wrote: "The real cause of our present unrest is the rapidly changing dimensions of medical science." Changing dimensions inevitably entail changing responsibilities. Traditionally, the physician has stood by, waiting for something not under human control to happen to the individual, which more often than not it did. The first real departures from this time-hallowed approach arose when sanitation and immunization made it possible to prevent epidemics. Society acquired the ability to protect man from a wide variety of the extrinsic causes of disease. Society is now well on top of the environmental factors, plagues, and famines,

[3] Auerbach, C.: Chemical mutagenesis, Biol. Reviews **24**: 355, 1949.
[4] Boyland, E.: Mutagens, Pharmacol. Rev. **6**: 345, 1954.
[5] Barthelmess, A.: Mutagene Arzneimittel, Arzneimitt.-Forsch. **6**: 157, 1956.
[6] Westergaard, M.: Chemical mutagenesis in relation to the concept of the gene, Experientia **13**: 224, 1957.
[7] MacMahon, B., and Koller, E. K.: Ethnic differences in the incidence of leukemia, Blood **12**: 1, 1957.
[8] Lewis, E. B.: Leukemia and ionizing radiation, Science **125**: 965, 1957.
[9] Court Brown, W. M.: Gonad doses from diagnostic and therapeutic radiology, *in* Effect of radiation on human heredity, 1957, World Health Organization, Geneva, pp. 95–99.
[10] Wood, W. B.: The underlying cause of unrest in university medicine, J. A. M. A. **164**: 548, 1957.

which in the past have limited the growth and development of human populations. Ironically, however, the same cultural developments which have brought these blessings may pose as real a threat to man's biologic integrity as would any plague or famine. The threat is all the more dangerous because it is so subtle. There is urgent need for the development of a new kind of team, a team whose patient is society as a whole rather than the individuals of which it is composed. This team involves such diverse medical and nonmedical elements as the internist, the epidemiologist, the geographic pathologist, the psychiatrist, the cultural anthropologist, the sociologist and the geneticist. The task is a formidable one—*to define clearly the circumstances which permit man, with all his genetically imposed limitations, to function best and continue his organic evolution.* It is really an awesome responsibility, but who will accept it if medicine fails to take the initiative?

There is only one alternative in sight, as witness the space devoted in the commercial exhibits to the ataraxics. Their increasing use in other than psychotic patients is a tacit admission that we have created a culture we are having difficulty living with. But while drugs are wonderful crutches, Mother Nature does have a way of reasserting herself. We may be able today, with the help of a prominent pharmaceutical house, to dial the mood we wish to allay, and read off the proper tranquilizer. I doubt very much if this is the answer for tomorrow. Beckman's statement on this subject seems particularly appropriate: "The continued promiscuous prescribing of tranquilizing drugs is to put the sign and seal of doom upon the human race as the highest of evolved creatures." [11]

Turning points in history, medical or otherwise, are seldom right angle bends shaped by single individuals, but curves shaped by many pressures. We are in one now. Despite the elusiveness of the problems with which this statement deals, it seems highly likely that at some point not far off, medicine, responding to either inward or outward pressures, must attempt to come to grips with the developments just enumerated.

Summary

Man is being thrust at a constantly accelerating rate into new situations. But at the very time that continuing organic evolution is called for, a number of factors which may actually be thwarting the evolutionary process may be recognized. Some of the biologic problems posed by these developments have been discussed.

James V. Neel, M.D.

[11] Beckman, H.: An end to tranquilization! Marquette M. Rev. **22**: 114, 1957.

REVIEWS

Hemorrhagic Diseases. By ARMAND J. QUICK, Ph.D., M.D., Professor of Biochemistry, Marquette University School of Medicine. 451 pages; 16 × 24 cm. Lea and Febiger, Philadelphia. 1957. Price, $9.50.

In this small attractive volume, Dr. Quick has attempted to bring up to date a discussion of hemorrhagic diseases in the light of the many recent developments. His extensive experience allows an authoritative approach. His informal narrative style makes reading this difficult subject pleasant and easy.

The book is divided into two parts. The first deals with clinical disorders of hemostasis, grouped in chapters according to the basic defect. An introductory chapter describes the historical development of current concepts of hemostasis. Physiologic aspects of blood coagulation are discussed in one chapter in an effort to avoid cluttering the remainder with some of the confusing issues. The chapters on hemorrhagic diseases emphasize clinical features.

The second part describes 25 technics which the author has found valuable in studying hemorrhagic diseases. Applications and interpretations are discussed briefly.

In dealing with a subject as controversial as that of hemostasis and blood coagulation, there are obviously many theories, concepts, and confusing terminologies. Dr. Quick has used his own, while at the same time recognizing the work of other investigators. The book is written primarily for those in clinical medicine rather than for the strict academician, and will be of interest to many, particularly hematologists and clinical pathologists. It should serve as a valuable reference book for the practicing physician confronted with a hemorrhagic disorder.

C. L. SPURLING, M.D.

The Clinical Aspects of Arteriosclerosis. By SEYMOUR H. RINZLER, M.D., F.A.C.P., Associate Physician, Beth Israel Hospital; Instructor in Pharmacology, Cornell University Medical College, New York, N. Y. 339 pages; 18 × 26 cm. Charles C Thomas, Springfield, Illinois. 1957. Price, $8.75.

The major part of this book is devoted to the cardiac aspects of arteriosclerosis, with a section on its cerebral, aortic, peripheral vascular, retinal, renal and pulmonary aspects. There is an introduction concerned with general considerations in arteriosclerosis. The author is well-read in the field and has contributed himself to knowledge concerning arteriosclerosis. There are many quotations from and references to work of others.

It is regrettable that the author at times does not draw conclusions or point out where the probable truth lies, rather than present material in an inconclusive fashion. Such statements would be of particular help to the general practitioner, for whom this book is intended, according to the preface. This inconclusiveness is noted in the section on diet and arteriosclerosis. Again, stress tests for coronary disease are described, but no specific recommendations are made concerning the choice of a test and, more important, no mention is made concerning contraindications for carrying out such a test. In the discussion of acute myocardial infarction, there are no specific recommendations concerning the duration of rest, whether in bed or chair, and no recommendations for the conduction of the patient during convalescence.

This book brings together in one volume a great deal of useful information concerning arteriosclerosis, with good illustrations, and extensive references to the literature. The omissions mentioned above have been cited because of their importance to the general practitioner for whom this volume is primarily intended.

S.S.

Drugs: Their Nature, Action and Use. By HARRY BECKMAN, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, etc. 728 pages; 26 × 18 cm. W. B. Saunders Company, Philadelphia. 1958. Price, $15.00.

This new textbook in pharmacology is modern, well organized and written in a style which reflects the felicity of diction of the author. Recent advances, new concepts and many important new drugs are included. Generic and trade names are given.

The book is divided into three parts: *Part I* delineates the role and reward of the pharmacologist. It orients the student regarding the relationship of pharmacology to the other basic medical sciences. *Part II* discusses the nature of drugs, their source, action and fate in the body as well as important clinical effects. *Part III* discusses the actions and clinical applications of drugs. In this section pharmacology is the chief subject matter and the basic principles and fundamental mechanisms of action are treated in a comprehensive manner. The descriptions are clear and completely adequate for the needs of the medical student. Selected references for further reading appear at the end of each chapter.

Dr. Beckman's book adequately reflects his broad experience as a teacher of pharmacology and his skill as a medical writer.

JOHN C. KRANTZ, JR.

Diabetes as a Way of Life. By T. S. DANOWSKI, M.D., Renziehausen Professor of Research Medicine, University of Pittsburgh School of Medicine. 177 pages; 13 × 19.5 cm. Coward-McCann, Inc., New York. 1957. Price, $3.50.

This useful addition to the armamentarium of the physician by the author of *Diabetes Mellitus with Emphasis on Children and Young Adults* is an outgrowth of a booklet used to educate his patients and their families. Not too erudite for many parents, adolescent and adult patients, it appears to be an excellent summary also for medical technologists, dietitians, medical social workers and nurses. Unlike some books written for similar readers, other opinions and approaches are presented in addition to those of the author.

All physicians will agree on the therapeutic importance of the intelligent acceptance by the patient of a chronic disorder as a "way of life." Some, however, will disagree with the lack of emphasis upon the use of single scale insulin syringes to avoid patient errors in insulin dosage. The implication that (p. 76) certain renal complications may lessen the insulin need of some diabetics may require further investigation. The statement that (p. 135) the well regulated diabetic need have no fear of developing 'neuritis' may be premature. The author urges the periodic elective hospitalization of diabetics for their instruction, evaluation and emotional support. Unfortunately, such an ideal, in most communities, cannot be realized because of chronic numerical inadequacy of hospital inpatient facilities.

The unusual virtues of this book consist of its open recognition and acceptance of the emotional and social problems of diabetic patients, their families and friends, its lack of hostility and punitiveness toward the patients, and its lack of sentimentality in its reassurance and warm scientific frankness.

P. F.

Our Nuclear Adventure. By D. G. ARNOTT. 170 pages; 13.5 × 22 cm. Philosophical Library, Inc., New York. 1958. Price, $6.00.

Medical men will feel greater kinship with this author than with a pure physicist. Mr. Arnott is a biologist whose interest in nuclear physics has led him to his current position, which includes an advisory capacity to clinicians involved in the use of radioisotopes at the University of London.

The book was written for those without special knowledge of nuclear energy. It takes the optimistic view that our civilization will not be destroyed by nuclear war. It tries to define the problems and hazards of nuclear power and to answer the technical questions that arise. There are references to some of the political and social implications of this new power.

The author feels that the present management of these affairs is haphazard and often ruled by political and commercial considerations. His book is an attempt to dispel ignorance on the part of the laity in order to promote more effective control and usage of radioisotopes. The book is well written and conveys sincere concern for our present danger. No bibliography is included.

ROBERT C. DUVALL

Endocrine Pathology of the Ovary. By JOHN MCLEAN MORRIS, M.D., and ROBERT E. SCULLY, M.D. 151 pages; 17.5 × 25.5 cm. C. V. Mosby Company, St. Louis. 1958. Price, $8.50.

Although there has been a great increase in interest in endocrinology as it relates to the field of reproduction in recent years, there is a paucity of collected material in book form. *Endocrine Pathology of the Ovary* is a needed and timely contribution to the gynecological literature.

The initial phase of this book deals with the fundamental aspects of the embryologic development of the gonads, both male and female. From this the authors develop a reasonable logic concerned with the hormonal potentialities of ovarian tumors. Specific references in regard to the several more commonly used hormonal assays are included. The current concepts of feminization, defeminization and masculinization are reviewed.

The second phase of the book is concerned with specific endocrine producing lesions of the ovary. The illustrations are superb. There is no finer collection of photomicrographs to be found in any book of general or specialized pathology. Clinical aspects of the several hormonal secreting ovarian neoplasms are presented with excellent clarity.

The authors are to be commended for this scholarly presentation of the interesting and important hormone secreting ovarian tumors.

ARTHUR L. HASKINS, M.D.

Therapeutic Heat. Volume II of Physical Medicine Library. Edited by SIDNEY LICHT, M.D. 466 pages; 15.5 × 23.5 cm. Elizabeth Licht, Publisher, New Haven, Conn. 1958. Price, $12.00.

There has been a need for an up-to-date complete reference book on thermotherapy for the teaching of physiatrists and for the library of practicing specialists in Physical Medicine. Well-qualified men have contributed authoritative discussions on the physics, biophysics, and physiology in the many forms of heat used in Physical Therapy Departments, Doctors' offices, and in the home. The book is organized in the familiar pattern of basic science chapters followed by a discussion of methods and then clinical application.

The discussions of methods are clear and concise and should be helpful to physical therapists and physicians other than specialists in Physical Medicine who use heat in its various forms in their practice.

The chapters on clinical application, for the most part, reflect the present altered and practical emphasis in Physical Therapy, which is directed more toward active and purposeful exercise, rather than passive and palliative treatment (heat and massage). Unfortunately, this is not true of the chapter on neuromuscular disorders. The details of technic and theoretical basic science will be welcomed by the specialist

in the field of Physical Medicine, those training in the field, and as a reference to practicing clinicians. The appendix has an excellent discussion of medical legal aspects of therapeutic heat.

This book will prove useful not only to physicians, but to physical therapists as well. It is well organized so that one can readily use it as a reference book.

F. I. M.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Abortion in the United States: A Conference Sponsored by the Planned Parenthood Federation of America, Inc. at Arden House and The New York Academy of Medicine. Edited by MARY STEICHEN CALDERONE, M.D., M.S.P.H., Medical Director, Planned Parenthood Federation of America, Inc.; introduction by M. F. ASHLEY MONTAGU. 224 pages; 24 × 16 cm. 1958. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $5.50.

Annual Review of Medicine. Volume 9. DAVID A. RYTAND, Editor, Stanford University School of Medicine; and WILLIAM P. CREGER, Associate Editor, Stanford University School of Medicine. 530 pages; 23 × 15.5 cm. 1958. Annual Reviews, Inc., Palo Alto, California. Price, $7.00 (foreign shipment, $7.50).

Applied Physiology of the Eye. By H. WILLOUGHBY LYLE, M.D., F.R.C.S.; assisted by T. KEITH LYLE, C.B.E., M.A., M.D., M.Chir., M.R.C.P., F.R.C.S. 341 pages; 23 × 14.5 cm. 1958. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, $9.00.

Aspects Actuels de la Biochimie des Acides Aminés et des Protéines. (Actualités Biochimiques, publiées sous la direction de Marcel Florkin et Jean Roche, No. 20.) By J. T. EDSALL. 156 pages; 24.5 × 16 cm. (paper-bound). 1958. Masson & Cie, Paris. Price, 2.000 fr.

Auscultation of the Heart. By ABE RAVIN, M.D., Associate Clinical Professor of Medicine, University of Colorado School of Medicine. 166 pages; 22.5 × 14.5 cm. 1958. The Year Book Publishers, Inc., Chicago. Price, $6.00.

Bases Physio-biologiques et Principes Généraux de Réanimation. (Agressologie—Réanimation—Hibernothérapie; collection publiée sous la direction de H. Laborit.) By H. LABORIT, avec la collaboration de M. CARA, D. JOUASSET, G. DUCHESNE et G. LABORIT. 273 pages; 23.5 × 16 cm. (paper-bound). 1958. Masson & Cie, Paris. Price, 2.600 fr.

Cancer Primitif du Foie et des Voies Biliaires: Études Anatomo-pathologiques et Biologiques. (Actualités Anatomo-pathologiques, publiées sous la direction de MM. J. Delarue et L. Frühling.) Par MM. FRED-C. ROULET, R. CAMAIN, MLLE. E. LEBRETON, MM. R. FAUVERT, L. HARTMANN, J. P. BENHAMOU, L. ORCEL, J. FEROLDI, E. H. BETZ et Y. LE GAL. 245 pages; 25.5 × 17 cm. 1958. Masson et Cie, Paris. Price, 3.600 fr.

Clinical Enzymology. Edited by GUSTAV J. MARTIN, Sc.D., Research Director, The National Drug Company, Philadelphia. 241 pages; 24.5 × 16 cm. 1958. Little, Brown and Company, Boston. Price, $6.00.

Diagnostic Medical Parasitology. By EDWARD K. MARKELL, Ph.D., M.D., Assistant Professor of Infectious Diseases, Division of Parasitology and Tropic Diseases, Department of Infectious Diseases, School of Medicine, University of California, Los Angeles; and MARIETTA VOGE, M.A., Ph.D., Assistant Professor of Infectious Diseases, Division of Parasitology and Tropic Diseases, Department of Infectious Diseases, School of Medicine, University of California, Los Angeles. 276 pages; 24 × 16 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $7.00.

Dietary Prevention and Treatment of Heart Disease. By JOHN W. GOFMAN, Ph.D., M.D., Donner Laboratory, University of California, Berkeley; ALEX V. NICHOLS, Ph.D., Donner Laboratory, University of California, Berkeley; and E. VIRGINIA DOBBIN, Senior Dietitian, E. V. Cowell Memorial Hospital, University of California, Berkeley. 256 pages; 21 × 14 cm. 1958. G. P. Putnam's Sons, New York. Price, $3.95.

Entzündung und Bluteiweisskörper. Von PRIV.-DOZ. DR. H. ODENTHAL; mit einem Geleitwort von PROF. DR. MED. F. GROSSE-BROCKHOFF. 115 pages; 23.5 × 15.5 cm. (paper-bound). 1958. Georg Thieme Verlag, Stuttgart; in the U.S.A. and Canada: Intercontinental Medical Book Corporation, New York. Price, kartoniert DM 19.50.

Facts About Pharmacy and Pharmaceuticals. 137 pages; 22.5 × 16 cm. (paper-bound). 1958. Health News Institute, New York. Price, Single copy, $1.25; quantity prices quoted on request.

Fibroses Pulmonaires et Insuffisances Respiratoires Chroniques. Par P. LAVAL; avec la collaboration de H. PAYAN, R. SIMONIN, J. L. ARDISSON, M. ARNOULD, J. COROLLEUR, M. GRÉGOIRE et P. ROCHU; préface du Pr. CH. MATTEI. 293 pages; 25 × 17 cm. (paper-bound). 1958. Masson & Cie, Paris. Price, 3.500 fr.

Glaucoma: Transactions of the Second Conference, December 3, 4, and 5, 1956, Princeton, N. J. Edited by FRANK W. NEWELL, M.D., Department of Surgery (Ophthalmology), The University of Chicago, Chicago, Illinois. 245 pages; 23.5 × 15.5 cm. 1957. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, $4.95.

Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. By HOWARD W. JONES, JR., M.D., Associate Professor of Gynecology, Johns Hopkins University School of Medicine, etc.; and WILLIAM WALLACE SCOTT, M.D., Ph.D., Professor of Urology, Johns Hopkins University School of Medicine, etc. 456 pages; 27 × 19.5 cm. 1958. The Williams & Wilkins Company, Baltimore. Price, $16.00.

Intestinal Obstruction. By CLAUDE E. WELCH, M.D., D.Sci. (Hon.); illustrated by MURIEL MCLATCHIE MILLER. 376 pages; 23.5 × 15.5 cm. 1958. The Year Book Publishers, Inc., Chicago. Price, $10.50.

Modern Trends in Endocrinology. Edited by H. GARDINER-HILL, M.D., F.R.C.P., Consultant Physician to St. Thomas's Hospital, London. 320 pages; 25 × 17 cm. 1958. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $13.50.

Modern Trends in Gastro-enterology (Second Series). Edited by F. AVERY JONES, M.D., F.R.C.P., Physician, Central Middlesex Hospital, etc. 458 pages; 25.5 × 17.5 cm. 1958. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $16.00.

Office Gastroenterology. By ALBERT F. R. ANDRESEN, M. D., Clinical Professor Emeritus of Medicine, State University of New York College of Medicine at New York City, etc. 707 pages; 24 × 16 cm. 1958. W. B. Saunders Company, Philadelphia. Price, $14.00.

Origin and Program of the U. S. National Health Survey: A Description of the Developments Leading to Enactment of the National Health Survey Act, and a Statement of the Policies and Initial Program of the Survey. Health Statistics from the U. S. National Health Survey, Series A-1. 36 pages; 26 × 20 cm. (paper-bound). 1958. U. S. Department of Health, Education, and Welfare, Washington, D. C. Price, 25¢ a copy, from Superintendent of Documents, Government Printing Office, Washington.

Peptic Ulcer and Psychoanalysis. Nervous and Mental Disease Monographs (No. 85). By ANGEL GARMA, M. D., Buenos Aires, Argentina. 143 pages; 23.5 × 16 cm. 1958. The Williams & Wilkins Company, Baltimore. Price, $6.00.

Polymyositis. By JOHN N. WALTON, M.D., M.R.C.P., First Assistant in Neurology, King's College, University of Durham, in the Royal Victoria Infirmary, Newcastle upon Tyne, etc.; and RAYMOND D. ADAMS, M.D., Bullard Professor of Neuropathology, Harvard University and Chief of the Neurological Service, Massachusetts General Hospital, Boston, Mass. 270 pages; 22.5 × 14.5 cm. 1958. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, $7.00.

Preliminary Report on Number of Persons Injured, United States, July-December 1957; Statistics on the Number of Persons Injured, the Number of Days of Disability Due to Injuries, and Class of Accident. Based on Data Collected in Household Interviews During July-December 1957. Health Statistics from the U. S. National Health Survey, Series B-3. 32 pages; 26 × 20 cm. (paper-bound). 1958. U. S. Department of Health, Education, and Welfare, Washington, D. C. Price, 30¢ a copy, from Superintendent of Documents, Government Printing Office, Washington.

Preliminary Report on Volume of Dental Care, United States, July-September 1957: Statistics on Dental Visits, Interval Since Last Dental Visit, and Edentulous Persons Based on Data Collected by Household Interviews During July, August, and September 1957. Health Statistics from the U. S. National Health Survey, Series B-2. 22 pages; 26 × 19.5 cm. (paper-bound). 1958. U. S. Department of Health, Education, and Welfare, Washington, D. C. Price, 25¢ a copy, from Superintendent of Documents, Government Printing Office, Washington.

Proceedings of the Sixth International Congress of the International Society of Hematology, Boston—August 27–September 1, 1956. Prepared and edited by the Publications Committee of the VIth INTERNATIONAL CONGRESS OF HEMATOLOGY: W. BAKER, W. C. BOYD, W. DAMESHEK, C. P. EMERSON, P. S. GERALD, R. B. PENNELL, A. RICHARDSON JONES, Chairman, Boston, Massachusetts; with the assistance of SHIGEYASU AMANO, Japan; MOISES CHEDIAK, Cuba; J. V. DACIE, England; J. DAUSSET, France; GIOVANNI DI GUGLIELMO, Italy; MICHEL ABU JAMRA, South America; SVEN MOESCHLIN, Switzerland; TADEUSZ TEMPKA, Poland; and LEANDRO M. TOCANTINS, U.S.A. 930 pages; 26 × 17.5 cm. 1958. Grune & Stratton, New York. Price, $25.00.

Recent Advances in Oto-laryngology. 3d Ed. By F. BOYES KORKIS, M.B., Ch.B. (N.Z.), D.I.O. (Eng.), F.R.C.S. (Ed.), F.R.C.S. (Eng.), Surgeon and Dean, Metropolitan Ear, Nose and Throat Hospital, etc. 438 pages; 21 × 14 cm. 1958. Little, Brown and Company, Boston. Price, $12.00.

Regional Ileitis. 2nd Revised Ed. By BURRILL B. CROHN, M.D., Consulting Gastroenterologist, Mount Sinai Hospital, New York; and HARRY YARNIS, M.D., Associate in Medicine for Gastroenterology, Mount Sinai Hospital, New York; with special contributions by RICHARD H. MARSHAK, M.D., and DAVID A. TURNER, Ph.D. 239 pages; 22 × 14 cm. 1958. Grune & Stratton, New York. Price, $7.25.

Research and Education in Rheumatic Diseases: Transactions of the Second National Conference at National Institutes of Health, Bethesda, Maryland, December 1, 1956. Edited by JOSEPH J. BUNIM, M.D., Clinical Director, National Institute of Arthritis and Metabolic Diseases. 156 pages; 24 × 15.5 cm. 1957. Arthritis and Rheumatism Foundation in cooperation with National Institute of Arthritis and Metabolic Diseases, Public Health Service, U. S. Department of Health, Education, and Welfare, New York. Distributed free to a selected list of specialists and to medical libraries. Supply practically exhausted.

A Search for Man's Sanity: The Selected Letters of Trigant Burrow, With Biographical Notes. Prepared by the EDITORIAL COMMITTEE OF THE LIFWYNN FOUNDATION, WILLIAM E. GALT, Chairman; foreword by SIR HERBERT READ. 615 pages; 22 × 15 cm. 1958. Oxford University Press, New York. Price, $8.75.